

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,  
Plaintiff,  
v.  
MSN LABORATORIES PRIVATE  
LIMITED, et al.,  
Defendants.

J. Caleb Boggs Courthouse  
844 North King Street  
Wilmington, Delaware

Wednesday, October 25, 2023  
8:30 a.m.  
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP  
BY: ANTHONY D. RAUCCI, ESQUIRE  
BY: JACK B. BLUMENFELD, ESQUIRE

-and-

WILMERHALE  
BY: KEVIN S. PRUSSIA, ESQUIRE  
BY: LISA J. PIROZZOLO, ESQUIRE  
BY: AMY KREIGER WIGMORE, ESQUIRE  
BY: JONATHAN A. COX, ESQUIRE  
BY: KEVIN M. YURKERWICH, Ph.D.

For the Plaintiff

1 APPEARANCES CONTINUED:

2 HEYMAN ENERIO GATTUSO & HIRZEL LLP  
3 BY: DOMINICK GATTUSO, ESQUIRE

4 -and-

5 WINSTON & STRAWN LLP  
6 BY: GEORGE LOMBARDI, ESQUIRE  
7 BY: BRYCE COOPER, ESQUIRE  
8 BY: KURT A. MATHAS, ESQUIRE  
9 BY: ELIZABETH GRDEN, ESQUIRE  
10 BY: KEVIN BOYLE, ESQUIRE  
11 BY: BRIAN O'GARA ESQUIRE

For the Defendants

Also Present:

Dr. Kondal Reddy Bairy

\*\*\* PROCEEDINGS \*\*\*

08:18:06

08:18:06 12

08:20:27

08:20:27 13

08:30:57 14

08:30:57 15

08:30:59 16

08:31:08 17

08:31:09 18

08:31:12 19

08:31:13 20

08:31:15 21

08:31:17 22

08:31:23 23

08:31:26 24

08:31:28 25

DEPUTY CLERK: All rise. Court is now in  
session. The Honorable Richard G. Andrews presiding.

THE COURT: All right. Good morning, everyone.  
Please let's continue.

MS. PIROZZOLO: Thank you, Your Honor. One  
housekeeping matter, we inadvertently put up the wrong  
version of the slide that --

THE COURT: That's right. I remember.

MS. PIROZZOLO: -- Dr. Myerson referenced, and  
I'd agree with Mr. Lombardi that Lines 18 to 19 of Page 700  
of the transcript could be stricken.

THE COURT: All right. Well, I will strike  
those two lines, and I'm sure the court reporter will take

Myerson - Direct (Continued)

08:31:33 1 care of it.

08:31:35 2 MS. PIROZZOLO: Thank you, Your Honor.

08:31:36 3 DIRECT EXAMINATION (Continued)

08:31:36 4 BY MS. PIROZZOLO:

08:31:38 5 Q. Good morning, Dr. Myerson.

08:31:39 6 A. Good morning.

08:31:41 7 Q. Now, Dr. Lepore and Dr. Donovan mentioned several

08:31:44 8 references offering your obviousness opinions.

08:31:47 9 MS. PIROZZOLO: Could we put up Slide 13 of your  
08:31:50 10 presentation?

08:31:50 11 BY MS. PIROZZOLO:

08:31:53 12 Q. Do any of the references discussed by Drs. Donovan  
08:31:57 13 and Lepore teach the method for synthesizing cabozantinib  
08:32:00 14 (L)-malate that's disclosed in the '349 patent?

08:32:03 15 A. No.

08:32:04 16 Q. Do any of the references discussed by Drs. Donovan  
08:32:08 17 and Lepore teach that 1-1 could be a process impurity or a  
08:32:12 18 degradation process in the synthesis of cabozantinib  
08:32:17 19 (L)-malate?

08:32:17 20 A. No.

08:32:19 21 Q. Do any of the references discussed by Drs. Donovan  
08:32:23 22 and Lepore teach that the 1-1 compound was genotoxic?

08:32:27 23 A. No.

08:32:28 24 Q. Do any of the references discussed by Drs. Donovan  
08:32:32 25 and Lepore describe a formulation of cabozantinib (L)-malate

Myerson - Direct (Continued)

08:32:36 1 essentially free of the 1-1 impurity?

08:32:39 2 A. No.

08:32:40 3 MS. PIROZZOLO: Now, let's look more closely at  
08:32:42 4 the Brown reference which is in -- at Tab 10 of your binder,  
08:32:47 5 and it's Defendants' Exhibit 291. And if we can put that  
08:32:53 6 up.

08:32:53 7 BY MS. PIROZZOLO:

08:32:57 8 Q. This is the reference that Drs. Lepore and Donovan  
08:32:59 9 referred to; correct?

08:33:00 10 A. Yes.

08:33:01 11 Q. What is Brown directed to?

08:33:04 12 A. It's directed to the malate salt of cabozantinib and  
08:33:11 13 discloses two crystalline forms of the malate salt.

08:33:14 14 Q. Does Brown suggest that one with -- the 1-1 impurity  
08:33:18 15 should be minimized in its synthesis of cabozantinib  
08:33:22 16 (L)-malate?

08:33:22 17 A. It does not.

08:33:24 18 Q. Does Brown suggest that the 1-1 is a harmful  
08:33:28 19 impurity?

08:33:28 20 A. It does not.

08:33:30 21 Q. Now, Brown refers to the 1-1 compound; correct?

08:33:34 22 A. Yes.

08:33:36 23 Q. Dr. Lepore has offered the opinion that a skilled  
08:33:39 24 artisan would be motivated to control for 1-1 because it is  
08:33:42 25 a starting material in the Brown synthesis.

Myerson - Direct (Continued)

08:33:47 1 Do you recall that?

08:33:47 2 A. I do.

08:33:49 3 Q. Do you agree with that opinion?

08:33:50 4 A. I do not.

08:33:52 5 Q. Could you explain why not?

08:33:53 6 A. Yes. Well, of course, starting materials can carry

08:34:00 7 through to the final product, but as we heard from

08:34:04 8 Dr. MacMillan, we have a continuous process with multiple

08:34:10 9 steps. 98 percent of the 1-1 starting material is used up

08:34:16 10 at the beginning of the first step, and then there are

08:34:20 11 multiple purification processes and other steps with

08:34:24 12 purification processes, thus that at the end of the fifth

08:34:28 13 step, we would not expect any significant amount of 1-1 to

08:34:34 14 carry through. We just would expect it to be de minimis.

08:34:39 15 Q. Would a skilled artisan looking at Brown understand

08:34:43 16 that the 1-1 impurity forms as a degradation process during

08:34:47 17 synthesis?

08:34:48 18 A. No. Again, as we heard from Dr. MacMillan, that

08:34:53 19 would not be expected by a person of ordinary skill.

08:34:58 20 Q. Now, Brown refers to the process that you discussed

08:35:01 21 earlier that Exelixis referred to as the A- 2 process;

08:35:06 22 correct?

08:35:06 23 A. That's correct.

08:35:09 24 Q. Is Example 1 in Brown that Dr. Lepore discussed

08:35:14 25 different from the synthetic scheme for making cabozantinib

Myerson - Direct (Continued)

08:35:19 1 (L)-malate that's disclosed in the '349 patent?

08:35:22 2 A. Oh, yes. It's significantly different.

08:35:27 3 Q. Now, let's turn -- and could you describe what you  
08:35:31 4 view as the key differences?

08:35:32 5 A. Well, there are multiple differences, but the key  
08:35:36 6 difference is that the step in the Brown process that goes  
08:35:42 7 from 1-2 to 1-3 was eliminated. There's no 1-3. You go  
08:35:50 8 directly from 1-2 to 1-4. In addition, changes to the  
08:35:55 9 solvent and temperature of the salt formation step were  
08:35:58 10 made, both of those are significant changes. There are  
08:36:01 11 other changes as well.

08:36:03 12 MS. PIROZZOLO: Now, let's turn to Paragraph 97  
08:36:05 13 of Brown.

08:36:05 14 BY MS. PIROZZOLO:

08:36:11 15 Q. Dr. Lepore testified that Paragraph 97 of Brown  
08:36:16 16 describes cabozantinib (L)-malate that is essentially free  
08:36:19 17 of the 1-1 impurity.

08:36:22 18 Do you agree with that?

08:36:23 19 A. I do not.

08:36:26 20 Q. Could you explain why not?

08:36:28 21 A. Well, if we look at the paragraph, it's really  
08:36:32 22 focused on crystalline form purity. That is, how much of  
08:36:36 23 one crystalline form is present in a mixture of crystalline  
08:36:39 24 forms. And that's the focus of this.

08:36:43 25 Now, what I will agree that it does say at the

Myerson - Direct (Continued)

08:36:46 1 very end, that some process in the purities could be  
08:36:53 2 present, but even with that, you can still -- it doesn't  
08:36:55 3 disclose something that would essentially a 1-1 impurity,  
08:36:56 4 but even with that, you can still -- it doesn't disclose  
08:36:59 5 something that would be essentially free of the 1-1  
08:37:02 6 impurity.

08:37:03 7 Q. Could you explain why, even though it refers to  
08:37:05 8 process impurities, it doesn't disclose anything --  
08:37:08 9 something that would be essentially free of the 1-1  
08:37:11 10 impurity?

08:37:11 11 A. Right. Because we're talking that the 1-1 impurity,  
08:37:15 12 essentially free means that we have 0.02 percent of the 1-1  
08:37:21 13 impurity. And you could have something that met these  
08:37:25 14 crystalline form purities still had 0.02 percent of the 1-1  
08:37:31 15 purity. In fact, even if you say about 100 percent, about  
08:37:36 16 100 percent encompasses 99.98 percent. So, I don't see how  
08:37:41 17 this could tell somebody that it would be essentially free  
08:37:45 18 of the 1-1 impurity.

08:37:48 19 Q. Does Brown disclose pharmaceutical compositions of  
08:37:54 20 cabozantinib (L)-malate that are essentially free of the 1-1  
08:37:57 21 impurity?

08:37:57 22 A. It does not.

08:38:00 23 MS. PIROZZOLO: Now, turning to slide -- well,  
08:38:08 24 let me strike that.

08:38:08 25 BY MS. PIROZZOLO:

Myerson - Direct (Continued)

08:38:09 1 Q. To summarize, what are your opinions on the key  
08:38:11 2 differences between Brown and the '349 patent?

08:38:17 3 A. Well, the first key difference is that the '349  
08:38:21 4 patent has a different synthetic process which was designed  
08:38:25 5 to minimize the 1-1 impurity at very low levels.

08:38:30 6 Secondly, the '349 discloses formulation of the  
08:38:37 7 1-1 impurity that's essentially free -- I'm sorry,  
08:38:41 8 formulation of cabozantinib (L)-malate which is essentially  
08:38:45 9 free of the 1-1 impurity. Brown does not disclose any  
08:38:49 10 specific formulation or discuss specific formulations.

08:38:54 11 Q. Okay. So, let's turn to Dr. Lepore's inherency  
08:39:01 12 opinion.

08:39:01 13 MS. PIROZZOLO: And go to slide 15, please.

08:39:01 14 BY MS. PIROZZOLO:

08:39:04 15 Q. Looking at the first point on this slide, for the  
08:39:11 16 asserted claim of the '349 patent, what must be essentially  
08:39:15 17 free of the 1-1 impurities?

08:39:17 18 A. The pharmaceutical composition.

08:39:20 19 Q. Now, if an API has less than 200 PPM of 1-1, will the  
08:39:27 20 formulated composition necessarily be free of the 1-1  
08:39:30 21 impurity?

08:39:30 22 A. No, because as we've seen, the process of blending  
08:39:36 23 with excipients and making it into a drug product can result  
08:39:41 24 in increase in the 1-1 impurity. Thus, it's possible to  
08:39:44 25 start with an API that's essentially free, but end up with a



Myerson - Direct (Continued)

08:39:49 1 drug product that's not essentially free due to the  
08:39:51 2 additional formation of the 1-1.

08:39:54 3 Q. Did Exelixis' own work show that the 1-1 impurity  
08:39:57 4 could form during manufacturing of a drug product?

08:40:00 5 A. Yes.

08:40:02 6 Q. Could you explain why that's your opinion?

08:40:06 7 A. Well, certainly. We first saw the excipient  
08:40:08 8 compatibility studies which showed that the 1-1 could --  
08:40:14 9 would increase in contact with a number of different  
08:40:16 10 excipients. Secondly, we see the Exelixis studies that  
08:40:20 11 showed that the 1-1 impurity would increase when exposed to  
08:40:26 12 temperature, heat -- heat, moisture, and potentially  
08:40:33 13 physical force, which are used in manufacturing of tablets  
08:40:37 14 and capsules.

08:40:39 15 Q. Now, let's turn to your second point.

08:40:48 16 Do you agree with Dr. Lepore that the synthetic  
08:40:52 17 process in Brown does not inherently result in less than  
08:40:55 18 200 PPM?

08:40:56 19 A. I do not.

08:40:58 20 MS. PIROZZOLO: Let's pull up Brown, Defendants'  
08:41:03 21 Exhibit 291, at paragraph 213.

08:41:03 22 BY MS. PIROZZOLO:

08:41:08 23 Q. What does this paragraph in Brown teach?

08:41:11 24 A. Okay. I'm just getting it on my...

08:41:19 25 Q. I think it's on the screen, if that's...

Myerson - Direct (Continued)

08:41:21 1 A. Yeah. I -- it's easier for me to read.

08:41:23 2 Q. Okay.

08:41:24 3 A. What tab is that? I'm sorry.

08:41:26 4 Q. It's -- let me get it. It's Tab 10.

08:41:33 5 A. Tab 10. And paragraph 213.

08:41:43 6 Yes. Okay. Thank you.

08:41:46 7 Q. What does this paragraph in Brown teach?

08:41:48 8 A. Well, it actually specifically says, "The foregoing  
08:41:55 9 disclosure has been described in some detail by way of  
08:41:57 10 illustration and examples for purposes of clarity and  
08:42:00 11 understanding."

08:42:04 12 We skip a sentence and then it says, "However,  
08:42:06 13 it should be understood that many variations and  
08:42:10 14 modifications can be made while remaining within the spirit  
08:42:13 15 and scope of the invention. It will be obvious of one of  
08:42:16 16 skill in the art that changes and modifications can be  
08:42:18 17 practiced within the scope of is the appended claims.  
08:42:22 18 Therefore, it is to be understood that the above description  
08:42:25 19 is intended to be illustrative and not restrictive."

08:42:30 20 Q. Now, Dr. Lepore has testified that the Brown process  
08:42:37 21 inherently produces cabozantinib (L)-malate with less than  
08:42:42 22 200 PPM of the impurity.

08:42:46 23 MS. PIROZZOLO: Could you turn in your binder to  
08:42:48 24 Tab 11, which is Plaintiff's Exhibit 38.

08:42:51 25 THE WITNESS: Yes.

Myerson - Direct (Continued)

08:42:51 1 BY MS. PIROZZOLO:

08:42:53 2 Q. What is -- what does this document show?

08:42:56 3 A. This is a document from the Exelixis NDA for the  
08:43:03 4 capsules, and it talks about batch analysis.

08:43:07 5 MS. PIROZZOLO: Could you turn to Table 1 on  
08:43:09 6 Page 2 of Plaintiff's Exhibit 38?

08:43:13 7 THE WITNESS: Yes.

08:43:13 8 BY MS. PIROZZOLO:

08:43:14 9 Q. What does Table 2 -- what does Table 1 show?

08:43:18 10 A. It shows five lots of cabozantinib (L)-malate that  
08:43:26 11 were manufactured and it looks at test results for various  
08:43:34 12 impurities and overall purity.

08:43:36 13 Q. Okay. Now, Dr. Myerson, do you agree with Dr. Lepore  
08:43:44 14 that the synthetic process does not inherently result in  
08:43:47 15 less than 200 PPM of the 1-1 impurity?

08:43:50 16 A. I'm sorry. Could you repeat that, please?

08:43:53 17 Q. Do you agree with Dr. Lepore that the synthetic  
08:43:56 18 process in Brown does not inherently result in less than  
08:44:01 19 200 PPM of the 1-1 -- strike that.

08:44:06 20 Do you agree with Dr. Lepore that the Brown  
08:44:09 21 synthetic process inherently results in less than 200 PPM of  
08:44:14 22 the 1-1 impurity?

08:44:15 23 A. I do not.

08:44:16 24 MS. PIROZZOLO: Okay. And going back to Table 1  
08:44:20 25 in Plaintiff's Exhibit 38.

Myerson - Direct (Continued)

08:44:22 1 BY MS. PIROZZOLO:

08:44:22 2 Q. Could you explain why you disagree?

08:44:25 3 A. Well, of the -- of the five lots described there,  
08:44:32 4 four of them are made by the A-2 process. Those are the  
08:44:37 5 lots listed; Regis, Regis, Regis, and Girindus.

08:44:42 6 Now, the three Regis lots show non-detected  
08:44:46 7 amounts of the 1-1 impurity and since the limit of detection  
08:44:51 8 of this test was 200 PPM, that would indicate it was below  
08:44:56 9 200 PPM. While the Girindus batch showed a result of  
08:45:01 10 0.06 percent, which is 600 PPM, which is not below 200 PPM.

08:45:07 11 Q. Okay. Now, you mentioned the .06 percent being  
08:45:17 12 600 parts per million; is that right?

08:45:19 13 A. Correct.

08:45:20 14 Q. Now, Dr. Lepore has testified that the Girindus batch  
08:45:24 15 is not representative of the Brown process.

08:45:26 16 Do you agree with that?

08:45:27 17 A. I do not.

08:45:29 18 Q. Could you explain the basis of your disagreement with  
08:45:32 19 Dr. Lepore?

08:45:33 20 A. Yes. Well, first, the -- Exelixis in their  
08:45:40 21 submission to the FDA represented that the batches made by  
08:45:44 22 both the Regis and Girindus processes were made according to  
08:45:48 23 A-2, which is the Brown process -- I mean, the -- the Brown  
08:45:53 24 process.

08:45:55 25 In addition, while I agree the Girindus lot had

Myerson - Direct (Continued)

08:46:00 1 some planned deviations, those planned deviations still  
08:46:05 2 fall, in my opinion, within the scope of Brown.

08:46:10 3 Q. Now, you mentioned the deviations, but did you  
08:46:14 4 consider the deviations discussed by Dr. Lepore?

08:46:16 5 A. I did.

08:46:18 6 Q. Okay. What was the effect of the Girindus deviations  
08:46:24 7 in your opinion?

08:46:25 8 A. Well, all of these deviations were made with the  
08:46:30 9 purpose of both increasing yield and reducing the amount of  
08:46:34 10 impurities.

08:46:34 11 And, in fact, if we look at the total impurities  
08:46:39 12 at the bottom of this table, we'll see that the purest batch  
08:46:44 13 made of all these batches actually is the Girindus batch  
08:46:48 14 with 0.36 percent impurity. So, actually the planned  
08:46:53 15 deviations resulted in a purer batch of cabozantinib  
08:46:58 16 (L)-malate than was -- was obtained from the Regis batches.

08:47:04 17 Q. And how is that relevant to your opinion?

08:47:06 18 A. Well, it demonstrates that the deviations were made  
08:47:09 19 in such a way as to reduce the overall amount of impurities.  
08:47:14 20 In addition, if we look the deviations were done in steps  
08:47:18 21 that would not be expected to produce the 1-1 impurity.

08:47:23 22 Q. Now, in your opinion, do the deviations referenced by  
08:47:27 23 Dr. Lepore take the Girindus lot outside the scope of  
08:47:31 24 Example 1 in Brown?

08:47:32 25 A. No.

Myerson - Direct (Continued)

08:47:33 1 Q. Could you explain why not?

08:47:34 2 A. Again, because Example 1 -- Example 1 of Brown allows  
08:47:40 3 for deviation and I believe this is -- again, just falls in  
08:47:46 4 within the scope of Example 1.

08:47:49 5 Q. Now, turning from the Girindus batch to the Regis  
08:47:53 6 batches. Do you recall Dr. Lepore's testimony about GTI  
08:48:00 7 testing on those batches?

08:48:01 8 A. Yes.

08:48:02 9 Q. GTI specific.

08:48:04 10 Do you dispute the results of the GTI specific  
08:48:08 11 tests that Dr. Lepore discussed?

08:48:10 12 A. No. The GTI tests are very accurate.

08:48:15 13 MS. PIROZZOLO: Let's turn to Plaintiff's  
08:48:17 14 Exhibit --

08:48:17 15 THE COURT: And I'm sorry. I may have lost a  
08:48:21 16 thread of it here, but in terms of the three Regis batches  
08:48:27 17 actually producing the API with less than 200 parts per  
08:48:36 18 million, do you agree that -- that that's a fact?

08:48:42 19 THE WITNESS: Yes, certainly.

08:48:44 20 THE COURT: Okay.

08:48:46 21 MS. PIROZZOLO: Now, let's turn to Plaintiff's  
08:48:48 22 Exhibit 35, which is the Cometriq NDA.

08:48:51 23 Could you took look at Table 2 on Page 16?

08:48:55 24 THE WITNESS: Yes.

08:48:55 25 BY MS. PIROZZOLO:

Myerson - Direct (Continued)

08:48:57 1 Q. Does the information in this table inform your  
08:49:00 2 opinion on inherency?

08:49:03 3 A. Yes.

08:49:05 4 Q. Could you explain why?

08:49:06 5 A. Again, this is -- submitted to the FDA -- indicating  
08:49:12 6 that batches made by the A-2 process had within 35 and  
08:49:18 7 411 parts per million indicating that at least some batches  
08:49:26 8 had more than 200 parts per million.

08:49:30 9 Q. Does that inform your opinion as to whether the Brown  
08:49:35 10 process would necessarily produce cabozantinib (L)-malate  
08:49:39 11 inherently free of the 1-1 impurity?

08:49:42 12 A. It does.

08:49:42 13 Q. Could you explain why?

08:49:44 14 A. Again, it specifically says that -- well, that API  
08:49:50 15 made by the A-2 process could have as high as 411 ppms over  
08:49:55 16 the 1-1 impurity.

08:49:57 17 Q. Okay. Now, were you here when Dr. Lepore discussed  
08:50:00 18 what he called the Regis process?

08:50:02 19 A. Yes.

08:50:04 20 MS. PIROZZOLO: Can we pull up Dr. Lepore's  
08:50:09 21 Slide 14, please?

08:50:09 22 BY MS. PIROZZOLO:

08:50:12 23 Q. Now, Dr. Lepore' Slide 14 refers to Defendants'  
08:50:18 24 Exhibit 38; correct?

08:50:18 25 A. Yes.

Myerson - Direct (Continued)

08:50:21 1 MS. PIROZZOLO: Let's look at Exhibit 38, that's  
08:50:24 2 at Tab 23 in your binder.

08:50:24 3 BY MS. PIROZZOLO:

08:50:37 4 Q. What is Defendants' Exhibit 38?

08:50:38 5 A. That's an Exelixis document.

08:50:41 6 Q. Okay. Is Defendants' Exhibit 38 a Regis document?

08:50:45 7 A. No.

08:50:47 8 Q. Okay. What does Defendants' Exhibit 38 describe?

08:50:52 9 A. It describes information on the drug substance,  
08:50:57 10 different properties, and then it talks about the synthetic  
08:51:05 11 route for the preparation of XL184, which is cabozantinib.

08:51:09 12 Q. Were you here when Dr. Lepore testified about  
08:51:12 13 capsules containing XL184?

08:51:14 14 A. Yes.

08:51:16 15 MS. PIROZZOLO: Okay. Let's pull up Plaintiff's  
08:51:18 16 Exhibit 9 that Dr. Lepore referred to.

08:51:18 17 BY MS. PIROZZOLO:

08:51:22 18 Q. What is Exhibit 9?

08:51:23 19 A. Exhibit 9 -- done with that.

08:51:33 20 This is, again, from the -- it's an Exelixis  
08:51:48 21 document talking about the drug product of XL184 with  
08:51:55 22 cabozantinib (L)-malate in 25- and 100-milligram capsules.

08:52:00 23 Q. Was Defendants' Exhibit 9 in the prior art?

08:52:03 24 A. No.

08:52:05 25 Q. Does the prior art disclose capsules with the



Myerson - Direct (Continued)

08:52:08 1 formulation of the capsules in Exhibit 9?

08:52:11 2 A. No.

08:52:15 3 Q. Now, Dr. Lepore testified that even if Brown does not  
08:52:20 4 inherently teach the essentially free limitation, a person  
08:52:25 5 of ordinary skill would be motivated to modify Brown to  
08:52:28 6 obtain a pharmaceutical composition essentially free of the  
08:52:32 7 1-1 impurity.

08:52:34 8 Do you agree with Dr. Lepore on that?

08:52:36 9 A. I do not.

08:52:38 10 Q. Okay. Let's go to some of your reasons for  
08:52:43 11 disagreeing with Dr. Lepore.

08:52:45 12 Dr. Lepore testified that a skilled artisan  
08:52:49 13 would have been motivated to control for 1-1 during the  
08:52:53 14 synthesis of the API in Brown because it was a starting  
08:52:56 15 material.

08:52:58 16 Do you agree with that?

08:52:59 17 A. No. As I've already noted, because it's a starting  
08:53:03 18 material it's essentially mainly used up in the first step  
08:53:08 19 and then there are multiple purification steps, an  
08:53:16 20 additional synthesis step with purification steps.

08:53:19 21 By the time you make cabozantinib (L)-malate,  
08:53:21 22 you would expect very small amounts, if any, of detectable  
08:53:26 23 1-1 impurity, so there wouldn't be a motivation to control  
08:53:29 24 for it. Particularly since it hadn't been identified as a  
08:53:33 25 genotoxic impurity either.

Myerson - Direct (Continued)

08:53:36 1 Q. Now, Dr. Lepore testified that a skilled artisan  
08:53:40 2 would have been motivated to modify Brown because they would  
08:53:43 3 have expected the 1-1 impurity to form as a degradation  
08:53:47 4 product.

08:53:48 5 Do you recall that?

08:53:48 6 A. I do.

08:53:49 7 Q. Do you agree with Dr. Lepore?

08:53:51 8 A. No. As we heard from Dr. MacMillan, it would not be  
08:53:55 9 expected that the 1-1 impurity would form as a degradation  
08:53:59 10 product.

08:54:00 11 Q. And how does that affect motivation?

08:54:02 12 A. Well, you're not motivated to control for something  
08:54:05 13 that you don't think is going to form during your process.

08:54:11 14 Q. Now, Dr. Lepore testified that a skilled artisan  
08:54:14 15 would have been motivated to monitor --

08:54:18 16 MS. PIROZZOLO: And we can put up Slide 20.

08:54:18 17 BY MS. PIROZZOLO:

08:54:21 18 Q. -- and control for 1-1 because it has a quinoline  
08:54:24 19 structure. Do you agree with that?

08:54:25 20 A. No.

08:54:28 21 MS. PIROZZOLO: Can you put up Slide 20?

08:54:28 22 BY MS. PIROZZOLO:

08:54:31 23 Q. Why do you disagree with Dr. Lepore?

08:54:33 24 A. Well, many quinoline are actually drugs. I mean,  
08:54:39 25 cabozantinib is a quinolines. And there are lots and lots

Myerson - Direct (Continued)

08:54:43 1 of quinoline drugs, so clearly not all quinolines are  
08:54:47 2 problematic, they're not all genotoxic.

08:54:49 3 Q. Okay. Does cabozantinib have a quinoline structure?

08:54:52 4 A. It does.

08:54:53 5 Q. Is it genotoxic?

08:54:55 6 A. No.

08:54:56 7 Q. Could you turn to Tab 13 in your binder and put up  
08:54:59 8 the Nagao paper that Dr. Lepore discussed?

08:55:03 9 A. Yes.

08:55:07 10 Q. Does the Nagao paper discuss the compound at issue  
08:55:09 11 for the '349 patent?

08:55:11 12 A. I'm sorry. I couldn't hear that.

08:55:13 13 Q. Does the Nagao paper disclose the 1-1 compound at  
08:55:18 14 issue for the '349 patent?

08:55:20 15 A. No.

08:55:21 16 Q. Are all the quinoline structures reported in Nagao  
08:55:27 17 genotoxic?

08:55:27 18 A. No.

08:55:28 19 Q. Did Nagao describe any correlation between the  
08:55:32 20 structure of the quinolines and genotoxicity?

08:55:35 21 A. No.

08:55:36 22 Q. Can you explain why you don't see -- let me ask this:  
08:55:41 23 Do you see a correlation between a quinoline structure and  
08:55:45 24 genotoxicity in the Nagao paper?

08:55:48 25 A. No.

Myerson - Direct (Continued)

08:55:48 1 Q. Can you explain why not?

08:55:50 2 A. Well, if we look in the table in the Nagao paper --

08:55:59 3 Q. Is this Table 1?

08:56:00 4 A. Yes.

08:56:02 5 And if, for example, we look at Compound 16 and  
08:56:09 6 17, if we look, that the only difference between 16 and 17  
08:56:19 7 is that in Compound 17, we have an additional chloride on  
08:56:25 8 the -- on the wing on the bottom left. Otherwise, it's  
08:56:30 9 identical to 16.

08:56:32 10 And 17 is Ames negative and 16 is Ames positive.

08:56:39 11 Q. And how does that impact your opinion on whether a  
08:56:45 12 person of ordinary skill in the art would be motivated to  
08:56:46 13 control for the 1-1 impurity because it was a quinoline?

08:56:49 14 A. Well, again, you can't look at these structures and  
08:56:52 15 know if they're genotoxic or not. Very similar structures.  
08:56:56 16 Some will be genotoxic and some will not be genotoxic. So  
08:57:00 17 you only know when you do the AMES test.

08:57:02 18 MS. PIROZZOLO: So, let's turn to Defendants'  
08:57:02 19 Exhibit 272.

08:57:02 20 BY MS. PIROZZOLO:

08:57:06 21 Q. Which is Tab 14 in your binder.

08:57:12 22 Did you hear Dr. Lepore discuss Defendants'  
08:57:17 23 Exhibit 272?

08:57:17 24 A. I did.

08:57:19 25 Q. What is Defendants' Exhibit 272?

Myerson - Direct (Continued)

08:57:22 1 A. It's an EPA toxicological review of quinoline.

08:57:29 2 Q. Does the EPA toxicological review discuss the 1-1  
08:57:34 3 compound?

08:57:34 4 A. It does not.

08:57:37 5 Q. In your opinion, does the EPA toxicological review  
08:57:42 6 suggest that all of the quinoline structures are -- all  
08:57:45 7 quinoline structures are genotoxic?

08:57:47 8 A. No, it does not.

08:57:48 9 Q. Could you explain why not?

08:57:50 10 A. Again, it's really just talking about quinoline.  
08:57:52 11 It's not talking about all quinoline derivatives and  
08:57:55 12 structures.

08:57:56 13 Q. Okay. Let's turn to Plaintiff's Exhibit 299 at  
08:58:01 14 Tab 15. Is this a -- an article you considered in rendering  
08:58:06 15 your opinions in this case?

08:58:08 16 A. Yes.

08:58:09 17 Q. Could you explain what the article describes?

08:58:12 18 A. Yes. This is an article from RSC Advances and it's  
08:58:17 19 on recent advances in the chemistry and therapeutic  
08:58:20 20 potential of functionalized quinoline motifs, a review.

08:58:26 21 Q. Could you -- did this paper inform your opinions in  
08:58:29 22 this case?

08:58:29 23 A. Yes.

08:58:30 24 Q. Could you explain how?

08:58:31 25 A. Well, it talks about, in fact, quinolines that are

Myerson - Direct (Continued)

08:58:36 1 actually drugs. And if we go to Figure 1 in the paper.

08:58:42 2 Q. Is that at Page 3?

08:58:44 3 A. Yes. We have some examples of marketed drugs that  
08:58:49 4 are quinolines. And we see, we have antimalarials,  
08:58:53 5 antibacterials, anti-cancers, local anesthetics,  
08:58:58 6 anti-tubercular drugs, and these are just examples. There  
08:59:01 7 are actually a lot more quinolines that are marketed drugs.

08:59:07 8 Q. And how is this paper relevant to your opinions in  
08:59:11 9 this case?

08:59:12 10 A. Well, it just it generally shows that not all  
08:59:15 11 quinolines are genotoxic. In fact, many of them are useful  
08:59:19 12 as drugs.

08:59:20 13 Q. Did Dr. Lepore or Dr. Donovan provide any scientific  
08:59:25 14 explanation for why some quinoline structures are genotoxic  
08:59:29 15 and some are not?

08:59:30 16 A. No.

08:59:32 17 Q. In 2011, would a skilled artisan have been motivated  
08:59:35 18 to control for 1-1 simply because it was a quinoline?

08:59:39 19 A. No.

08:59:42 20 Q. Now, let's turn to the next motivation that  
08:59:48 21 Dr. Lepore provides to modify Brown.

08:59:52 22 These are regulatory guidances; correct?

08:59:55 23 A. Yes.

08:59:56 24 Q. Okay.

08:59:57 25 MS. PIROZZOLO: Let's put up Tab 18, which is

Myerson - Direct (Continued)

08:59:59 1 Defendants' Exhibit 291. Is -- sorry. Defendants'  
09:00:08 2 Exhibit 91.

09:00:08 3 BY MS. PIROZZOLO:

09:00:14 4 Q. Is Defendants' Exhibit 91 a guidance that Dr. Lepore  
09:00:19 5 discussed?

09:00:20 6 A. Yes.

09:00:21 7 Q. Could you describe your understanding of this  
09:00:23 8 particular guidance?

09:00:24 9 A. Yes. This is the guidance for industry on genotoxic  
09:00:28 10 and carcinogenic impurities in drug substances. And it  
09:00:33 11 talks about approaches, and it actually gives recommended  
09:00:36 12 limits for daily ingestion of these potential impurities in  
09:00:45 13 drug products.

09:00:46 14 Q. Okay. In 2011, would these guidelines have provided  
09:00:51 15 a skilled artisan with the motivation to control for the 1-1  
09:00:56 16 impurity in drug substances and products?

09:00:59 17 A. Only if they were aware that the 1-1 impurity was  
09:01:04 18 genotoxic.

09:01:05 19 Q. Okay. And at the time -- does anything in the prior  
09:01:08 20 art disclose that the 1-1 impurity was genotoxic?

09:01:11 21 A. No.

09:01:12 22 Q. Are these guidelines applicable if the impurity is  
09:01:15 23 not genotoxic?

09:01:16 24 A. No.

09:01:18 25 Q. Okay. Now, Drs. Donovan and Lepore also discussed a

Myerson - Direct (Continued)

09:01:25 1 few other guidelines. Do any of those guidelines refer to  
09:01:30 2 1-1 or describe methods for limiting byproducts or  
09:01:34 3 contaminants in cabozantinib (L)-malate?

09:01:36 4 A. No.

09:01:39 5 Q. So, let's go to the formulation references. Now,  
09:01:50 6 we've been focusing on the essentially free limitation. But  
09:01:55 7 Claim 3 of the '349 patent also requires certain classes of  
09:01:59 8 excipients; correct?

09:02:00 9 A. Correct.

09:02:02 10 Q. Do all pharmaceutical compositions have each of these  
09:02:05 11 four classes of excipients?

09:02:07 12 A. No.

09:02:08 13 Q. Why not?

09:02:09 14 A. Well, it really depends on the formulation and its  
09:02:13 15 purpose. So, for example, let's look at tablets. So,  
09:02:18 16 immediate release tablets, which are tablets that you take  
09:02:22 17 and -- and are supposed to dissolve in your body immediately  
09:02:26 18 always will have a disintegrant. But controlled-release  
09:02:30 19 tablets, which are designed to dissolve over time, don't  
09:02:38 20 necessarily have a disintegrant.

09:02:40 21 Capsules often do not have a disintegrant  
09:02:44 22 because you don't have to break apart a capsule. They  
09:02:48 23 sometimes can for other reasons, but that's -- this is one  
09:02:52 24 example. And, of course, not all formulations have to have  
09:02:59 25 glidants. If you have a well-flowing formulation, you don't



Myerson - Direct (Continued)

09:03:04 1 have to add a glidant. Generally, all capsules and -- all  
09:03:12 2 capsules and tablets will have fillers.

09:03:16 3 MS. PIROZZOLO: So, let's put up Claim 3 of the  
09:03:20 4 '349 patent.

09:03:20 5 BY MS. PIROZZOLO:

09:03:21 6 Q. Now, you heard Dr. Donovan testify that a skilled  
09:03:24 7 artisan would have been motivated to formulate cabozantinib  
09:03:29 8 (L)-malate as set forth in Claim 3.

09:03:32 9 Do you agree with that?

09:03:33 10 A. No.

09:03:38 11 Q. Could you explain why not?

09:03:39 12 A. Well, first of all, the formulation of any drug  
09:03:50 13 product requires you to understand the dosage form, the  
09:03:56 14 dose, and the physicochemical properties of the API. So,  
09:04:01 15 before you know how you're -- how you're going to formulate  
09:04:06 16 something, you have to do all that work. And then you can  
09:04:09 17 decide what classes of excipients you're going to employ.

09:04:13 18 Q. Okay. Have you heard the term "physicochemical  
09:04:16 19 properties"?

09:04:17 20 A. Yes.

09:04:18 21 Q. What physicochemical properties are important to  
09:04:22 22 formulation scientists?

09:04:24 23 A. Well, certainly the solubility, the permeability, the  
09:04:30 24 crystal size distribution, the crystal shape, the  
09:04:35 25 hygroscopicity, the carrying electric charge, the

Myerson - Direct (Continued)

09:04:38 1 compressibility, the flowability. There are probably some  
09:04:43 2 more but those are some of the main ones you're interested  
09:04:46 3 in.

09:04:47 4 Q. Is chemical stability important?

09:04:49 5 A. Yes.

09:04:49 6 Q. And why is that?

09:04:50 7 A. Well, chemical stability will determine whether the  
09:04:57 8 API is going to decompose, either due to interaction with  
09:05:02 9 the excipients or through the manufacturing process.

09:05:09 10 Q. What were some of the kinds of physicochemical  
09:05:12 11 properties that turned out to be important to how  
09:05:16 12 cabozantinib (L)-malate was formulated?

09:05:18 13 A. Well, first was the chemical stability. And second  
09:05:22 14 was the flowability.

09:05:24 15 Q. And why were those important?

09:05:25 16 A. Well, it turns out that cabozantinib (L)-malate could  
09:05:33 17 decompose to the 1-1 impurity when exposed to moisture,  
09:05:37 18 heat, and in the presence of certain excipients. In  
09:05:42 19 addition, it was poorly flowing. The API was poorly  
09:05:48 20 flowing.

09:05:48 21 Q. Okay. As of 2011, was the chemical stability of  
09:05:52 22 cabozantinib (L)-malate known in the prior art?

09:05:55 23 A. No.

09:05:57 24 Q. As of 2011, was the flowability of cabozantinib  
09:06:01 25 (L)-malate known in the prior art?

Myerson - Direct (Continued)

09:06:02 1 A. No.

09:06:04 2 Q. Okay.

09:06:05 3 MS. PIROZZOLO: Let's put up paragraph 82 of the  
09:06:08 4 Brown reference, Defendants' Exhibit 291.

09:06:08 5 BY MS. PIROZZOLO:

09:06:11 6 Q. At Tab 10 in your binder.

09:06:16 7 Dr. Donovan referred to paragraph 82 in Brown in  
09:06:20 8 her testimony. Do you recall that?

09:06:21 9 A. Yes.

09:06:23 10 Q. In your opinion, does paragraph 82 in Brown suggest  
09:06:27 11 formulating cabozantinib with a glidant?

09:06:30 12 A. No. A glidant is not a class of excipients that's  
09:06:33 13 listed in paragraph 82.

09:06:36 14 Q. Now, Dr. Donovan pointed in this paragraph to the  
09:06:39 15 excipient talc. Do you recall that?

09:06:42 16 A. I do.

09:06:43 17 Q. Is talc listed as a glidant in this paragraph?

09:06:46 18 A. No, it's listed as a lubricant.

09:06:49 19 Q. Okay. Have you seen any reference identified by  
09:06:54 20 Dr. Donovan that would motivate a skilled artisan to include  
09:06:58 21 a glidant?

09:07:00 22 A. To include a glidant in the --

09:07:03 23 Q. In a composition for cabozantinib (L)-malate?

09:07:05 24 A. No.

09:07:12 25 MS. PIROZZOLO: Now, let's pull up Defendants'

Myerson - Direct (Continued)

09:07:19 1 Exhibit 335, which is a patent application.

09:07:19 2 BY MS. PIROZZOLO:

09:07:23 3 Q. Do you recall Dr. Donovan discussing this patent  
09:07:26 4 application?

09:07:26 5 A. Yes.

09:07:28 6 Q. Does this patent application relate to cabozantinib?

09:07:32 7 A. No.

09:07:33 8 Q. What, at a general level, does this patent  
09:07:36 9 application relate to?

09:07:37 10 A. It relates to several other APIs that are tyrosine  
09:07:43 11 kinase inhibitors.

09:07:45 12 Q. Does the -- does the '081 application, which is  
09:07:49 13 Defendants' Exhibit 35 -- 335, teach that cabozantinib  
09:07:54 14 (L)-malate should be formulated with a filler, disintegrant,  
09:07:57 15 glidant, and lubricant?

09:07:59 16 A. No.

09:08:00 17 Q. Could you explain why not?

09:08:01 18 A. Well, it's because it's about different APIs, and  
09:08:05 19 different APIs have different properties. It doesn't really  
09:08:08 20 inform you if you have formulation for a completely  
09:08:14 21 different API how you're going to formulate a different API.  
09:08:18 22 Because you don't know -- the physicochemical properties are  
09:08:21 23 going to be different.

09:08:24 24 Q. Now, let's turn to the Lachman reference that

09:08:27 25 Dr. Donovan discussed which is Plaintiff's Exhibit 553A.

Myerson - Direct (Continued)

09:08:34 1 What is the Lachman reference?

09:08:36 2 A. This is a reference on pharmaceutical dosage forms.

09:08:43 3 Q. Did you hear Dr. Donovan testify that a skilled

09:08:46 4 artisan would be motivated by Lachman to formulate

09:08:50 5 cabozantinib (L)-malate with one or more fillers,

09:08:54 6 disintegrants, glidants and lubricants?

09:08:56 7 A. I did.

09:08:57 8 Q. Do you agree with Dr. Donovan's opinion?

09:08:59 9 A. No, Lachman is -- is a general reference on

09:09:02 10 formulation. And, of course, it talks about all classes of

09:09:06 11 excipients, but it also -- I think we saw the paragraph

09:09:10 12 already -- talks about how each formulation is a unique --

09:09:15 13 unique development project where you develop the formulation

09:09:21 14 based on the properties of the API.

09:09:25 15 MS. PIROZZOLO: So, let's turn to Page 76 of

09:09:27 16 Lachman, which is Page 3 of the PDF.

09:09:27 17 BY MS. PIROZZOLO:

09:09:33 18 Q. And looking at the sentence that begins with, "The

09:09:35 19 correct selection," is that what you're referring to,

09:09:39 20 Dr. Myerson?

09:09:39 21 A. Yes. "The correct selection and balance of excipient

09:09:43 22 materials for each active ingredient or ingredient

09:09:48 23 combination in a tablet formulation to achieve the desired

09:09:52 24 response (i.e. production of a safe, effective, and highly

09:09:58 25 reliable product) is not in practice a simple goal to

Myerson - Direct (Continued)

09:10:02 1 achieve."

09:10:04 2 Q. Do you agree with that statement in Lachman?

09:10:06 3 A. Yes.

09:10:07 4 Q. Could you explain why?

09:10:08 5 A. Well, because, again, each -- each formulation of a  
09:10:15 6 new API is a unique problem. And you might run into  
09:10:19 7 problems with flow or chemical stability or the ability to  
09:10:24 8 make a tablet that is -- doesn't break into pieces or is --  
09:10:35 9 has appropriate hardness, has the right dissolution  
09:10:38 10 properties. So, in fact, in my own experience, you go  
09:10:43 11 through lots and lots of iterations of excipients and blends  
09:10:47 12 and tablet press pressures and various other things to make  
09:10:53 13 a safe and effective and reliable formulation.

09:10:59 14 Q. So, we've talked about Brown, the '081 application  
09:11:04 15 and the Lachman reference. Do any of those, in your  
09:11:08 16 opinion, provide a motivation to formulate cabozantinib  
09:11:12 17 (L)-malate in the manner claimed in Claim 3 of the '349  
09:11:17 18 patent?

09:11:17 19 A. No.

09:11:19 20 MS. PIROZZOLO: Now, let's go to "Reasonable  
09:11:21 21 Expectation of Success." That's Slide 17 of your slides.  
09:11:21 22 BY MS. PIROZZOLO:

09:11:32 23 Q. Going to the first point, you heard Dr. Lepore  
09:11:37 24 testify that a skilled artisan would have simply added a  
09:11:41 25 recrystallization step to the synthetic process in Brown to

Myerson - Direct (Continued)

09:11:45 1 achieve an API that is essentially free of the 1-1 impurity.

09:11:50 2 Do you recall that?

09:11:50 3 A. I do.

09:11:52 4 Q. Do you agree with that?

09:11:52 5 A. I do not.

09:11:57 6 Q. Do you have an opinion -- strike that.

09:12:01 7 Are there any reasons that recrystallization

09:12:03 8 might be difficult in the context of cabozantinib

09:12:07 9 (L)-malate?

09:12:07 10 A. Yes. So, we're trying to reduce an impurity to below

09:12:13 11 200 PPM which is 0.02 percent. And the 1-1 impurity is

09:12:24 12 structurally similar to the API cabozantinib (L)-malate.

09:12:29 13 And often in crystallizations, when have you structurally

09:12:31 14 similar materials, the impurity substitutes in the

09:12:36 15 crystalline lattice as an impurity making it very difficult

09:12:39 16 to achieve that level of purification.

09:12:43 17 This is something I've been doing for more than

09:12:46 18 40 years. Crystallization is one of my main areas, and I've

09:12:50 19 seen this in many cases when you're trying to reduce

09:12:53 20 impurities to very low levels. They just won't be removed.

09:12:56 21 So you have to come up with a different separation process

09:12:59 22 or different synthetic process to achieve that level of

09:13:04 23 purity.

09:13:07 24 MS. PIROZZOLO: Let's call up Plaintiff's

09:13:10 25 Exhibit 494 which is Tab 21 in your binder.

Myerson - Direct (Continued)

09:13:10 1 BY MS. PIROZZOLO:

09:13:15 2 Q. What is Exhibit 494?

09:13:17 3 A. This is Chapter 3 of the *Handbook of Industrial*  
09:13:21 4 *Crystallization*, which is the second edition, which is a  
09:13:25 5 book I edited.

09:13:28 6 MS. PIROZZOLO: Let's turn to Figure 3.10 on  
09:13:32 7 Page 6.

09:13:32 8 BY MS. PIROZZOLO:

09:13:34 9 Q. What does Figure 3.10 show?

09:13:37 10 A. Well, this is a figure actually illustrating, among  
09:13:41 11 other things, the point I just made about substitution of  
09:13:45 12 impurities.

09:13:48 13 Q. Could you explain with reference to the circles in  
09:13:53 14 the figure how this would be relevant to recrystallizing  
09:13:58 15 cabozantinib (L)-malate?

09:13:58 16 A. Yes, so if the cabozantinib (L)-malate are the -- the  
09:14:04 17 white circles, and the 1-1 impurity is structurally  
09:14:09 18 similar -- it's A -- A can substitute in the crystalline  
09:14:15 19 lattice and, thus, is a substitutional impurity. And again  
09:14:21 20 substitutional impurities are impurities that have an  
09:14:23 21 affinity for the lattice, and they're very hard to reduce to  
09:14:27 22 very low levels.

09:14:29 23 Q. In your experience, is this kind of substitutional  
09:14:33 24 impurity common in crystallization of active pharmaceutical  
09:14:37 25 ingredients?



Myerson - Direct (Continued)

09:14:37 1 A. Yes, it's actually a problem that I work on quite  
09:14:41 2 often and companies ask me about quite often because it's --  
09:14:45 3 it's a difficult issue when you're trying to get an impurity  
09:14:48 4 that to these kinds of levels.

09:14:50 5 Q. How does this relate to your opinion as to whether a  
09:14:54 6 skilled artisan would have had a reasonable expectation of  
09:14:57 7 success in recrystallizing cabozantinib (L)-malate to obtain  
09:15:02 8 API essentially free of the 1-1 impurity?

09:15:05 9 A. Well, based on this mechanism, you would think they  
09:15:08 10 wouldn't have a reasonable expectation of success. In  
09:15:11 11 addition, of course, there's another reason. It's because  
09:15:16 12 the 1-1 impurity is a decomposition product of the API. So,  
09:15:21 13 when you -- it's just the act of redissolving it before you  
09:15:26 14 recrystallize could produce additional 1-1 impurity, making  
09:15:30 15 it even harder to get it essentially free.

09:15:35 16 MS. PIROZZOLO: Now, let's turn to Defendants'  
09:15:39 17 Exhibit 304 which is Tab 22 in your binder.

09:15:39 18 BY MS. PIROZZOLO:

09:15:46 19 Q. Did you hear Dr. Lepore discuss Defendants'  
09:15:50 20 Exhibit 304?

09:15:50 21 A. I did.

09:15:51 22 Q. What is Defendants' Exhibit 304?

09:15:54 23 A. It's a guidance for industry on manufacturing active  
09:16:00 24 pharmaceutical ingredients.

09:16:01 25 Q. Okay. In your opinion, would this reference motivate

Myerson - Direct (Continued)

09:16:06 1 a skilled artisan with reasonable expectation of success to  
09:16:11 2 add a recrystallization step to the Brown process to achieve  
09:16:15 3 cabozantinib (L)-malate essentially free of the 1-1  
09:16:18 4 impurity?

09:16:18 5 A. No.

09:16:20 6 Q. Could you explain your opinion?

09:16:22 7 A. Well, I mean, this -- this talks about purification  
09:16:26 8 and mentions that you can try to purify something via  
09:16:31 9 crystallization, but that wouldn't motivate a person to  
09:16:35 10 modify Brown because, first of all, they don't know the 1-1  
09:16:41 11 impurity is a decomposition product. And, as I note, a  
09:16:48 12 recrystallization step could be ineffective in this type of  
09:16:51 13 process. So, no, I don't believe it would.

09:16:55 14 MS. PIROZZOLO: Let's go to Slide 17.

09:16:55 15 BY MS. PIROZZOLO:

09:17:00 16 Q. So, we've talked about whether there would be a  
09:17:04 17 reasonable expectation of success for controlling 1-1 in the  
09:17:08 18 API of cabozantinib (L)-malate. Let's move to controlling  
09:17:14 19 1-1 in the pharmaceutical composition. Okay?

09:17:17 20 A. Yes.

09:17:19 21 Q. Without the information provided by the '349 patent,  
09:17:23 22 would a skilled artisan looking at the Brown reference have  
09:17:27 23 had a reasonable expectation of success in achieving  
09:17:30 24 cabozantinib (L)-malate composition with the claimed  
09:17:34 25 excipients free of the 1-1 impurity?

Myerson - Direct (Continued)

09:17:36 1 A. No.

09:17:36 2 Q. Could you explain why not?

09:17:38 3 A. Because the Brown process, first of all, would make  
09:17:45 4 API with variable amounts of the 1-1 impurity, including  
09:17:49 5 cases where the 1-1 impurity would already be greater than  
09:17:54 6 200 PPM. But even if it was below 200 PPM, it doesn't  
09:17:59 7 describe any information on excipient compatibility or any  
09:18:05 8 other thing that would allow you to formulate into a drug  
09:18:09 9 product that was essentially free.

09:18:16 10 Q. What were the properties of cabozantinib (L)-malate  
09:18:20 11 that were not in the prior art that would be needed to  
09:18:24 12 formulate cabozantinib (L)-malate essentially free of the  
09:18:27 13 1-1 impurity?

09:18:28 14 A. Well, first of all, you would have to know about its  
09:18:32 15 chemical stability. You'd have to understand whether it  
09:18:38 16 decomposed under various conditions, and you would also have  
09:18:43 17 to know the list of physicochemical properties I mentioned  
09:18:48 18 before, including the excipient compatibility studies, and  
09:18:56 19 because you're formulating it, you would still have to know  
09:18:58 20 about the flowability and the crystal size, crystal shape,  
09:19:04 21 all of those other things.

09:19:05 22 Q. Okay. Were those properties you just mentioned known  
09:19:09 23 in the prior art?

09:19:10 24 A. No.

09:19:13 25 Q. Without knowing about these properties and without

Myerson - Direct (Continued)

09:19:18 1 the benefit of the teaching of the '349 patent, could a  
09:19:21 2 person of skill have predicted how cabozantinib (L)-malate  
09:19:26 3 or levels of the 1-1 impurity would be affected by  
09:19:30 4 formulation?

09:19:30 5 A. No.

09:19:31 6 Q. Could you explain why not?

09:19:32 7 A. Again, there's no information on the effect of  
09:19:39 8 excipients, heat, moisture and processing conditions on the  
09:19:45 9 formation of the 1-1 impurity. In fact, we don't even know  
09:19:48 10 it's a degradation product, which is the key piece of  
09:19:51 11 information.

09:19:53 12 Q. Okay. Now, did you consider objective indicia in  
09:19:57 13 rendering your opinions in this case?

09:20:00 14 A. I did.

09:20:02 15 Q. What products -- and we can look at Plaintiff's  
09:20:05 16 Demonstrative Slide 3. What products practice Claim 3 of  
09:20:12 17 the '349 patent?

09:20:12 18 A. The tablets, Cabometyx, and the capsules, Cometriq.

09:20:21 19 Q. Did you consider whether there was a nexus between  
09:20:26 20 the objective indicia in Claim 3 of the '349 patent?

09:20:29 21 A. I did.

09:20:31 22 Q. What is your understanding of the nexus between the  
09:20:37 23 '349 patent and the objective indicia.

09:20:39 24 A. Well, the '349 patent was crucial because it  
09:20:42 25 disclosed a synthetic process to produce cabozantinib

Myerson - Direct (Continued)

09:20:48 1 (L)-malate at exceptionally low levels of the 1-1 impurity.  
09:20:52 2 That allowed it to be formulated into a drug product which  
09:20:58 3 continued to have low enough levels at of a 1-1 impurity  
09:21:02 4 after manufacturing and in storage to be sold and given to  
09:21:07 5 patients.

09:21:10 6 Q. Did you consider opinions of Dr. George?

09:21:13 7 A. I did.

09:21:14 8 Q. Okay. Dr. George will testify later, but did his  
09:21:19 9 opinions, as you understand them, inform your opinions in  
09:21:24 10 this case?

09:21:24 11 A. Yes, because Dr. George -- I relied on Dr. George for  
09:21:28 12 the usefulness of these formulated cabozantinib tablets and  
09:21:35 13 capsules for the use in treating cancer.

09:21:38 14 Q. Okay. Does the claimed invention as embodied in the  
09:21:43 15 Cabometyx product provide benefits over the prior art?

09:21:48 16 A. Yes. That's -- I'm relying on Dr. George for that.

09:21:57 17 Q. Were there benefits to the formulation that were  
09:22:01 18 relevant to patients?

09:22:04 19 A. Yes. Again, the formulation of the API that  
09:22:11 20 maintained formulation that was essentially free of the 1-1  
09:22:15 21 impurity is a key feature of this.

09:22:18 22 Q. Now, you understand Dr. George has offered opinions  
09:22:24 23 that Cabometyx is a clinical success.

09:22:29 24 Does that inform your opinions?

09:22:30 25 A. Yes. Of course. The -- if the drug is clinical -- a

Myerson - Direct (Continued)

09:22:36 1 clinical success, a key feature of that is that it had been  
09:22:42 2 formulated into a drug product. It can help people.

09:22:46 3 Q. Now, did you consider the opinions of Mr. Tate?

09:22:52 4 A. Yes.

09:22:54 5 Q. What opinions of Mr. Tate did you consider?

09:22:57 6 A. Commercial success.

09:22:59 7 Q. Does Mr. -- what was Mr. Tate's opinion on commercial  
09:23:04 8 success that we'll hear from him later?

09:23:07 9 A. Yes. That -- that these drug products have been  
09:23:12 10 commercially successful in the marketplace.

09:23:14 11 Q. Okay. How did Mr. Tate's opinions relate to your  
09:23:18 12 ultimate opinion on obviousness?

09:23:22 13 A. Again, these have -- for -- since I'm relying on  
09:23:27 14 Mr. Tate for commercial success, part of the commercial  
09:23:30 15 success has to be due to the successful formulation of the  
09:23:36 16 API into the drug product.

09:23:38 17 Q. Okay. Dr. Myerson, what is your conclusion  
09:23:41 18 concerning whether Claim 3 of the '349 patent is obvious?

09:23:44 19 A. It's my opinion that it is not obvious.

09:23:48 20 MS. PIROZZOLO: Thank you, Dr. Myerson. I have  
09:23:50 21 no further questions.

09:23:52 22 THE COURT: All right. Mr. Lombardi.

09:23:54 23 MR. LOMBARDI: Your Honor, may we pass up some  
09:23:58 24 binders?

09:23:58 25 THE COURT: Yeah. Sure.

Myerson - Cross

09:23:59 1 MR. LOMBARDI: Thank you.

09:24:08 2 CROSS-EXAMINATION

09:24:26 3 BY MR. LOMBARDI:

09:24:26 4 Q. Good morning, Dr. Myerson.

09:24:35 5 A. Good morning.

09:24:36 6 Q. My name is George Lombardi. We haven't met, have we?

09:24:39 7 A. Nice to meet you.

09:24:41 8 Q. Nice to meet you.

09:24:42 9 Sir, yesterday you spent a fair amount of time  
09:24:45 10 going through various processes that had been developed by  
09:24:50 11 Exelixis for the creation of the cabozantinib compound; is  
09:24:56 12 that right?

09:24:56 13 A. Correct.

09:24:57 14 Q. And you started with Process A-1, I think, that was  
09:25:02 15 the first one they had.

09:25:04 16 A. Yes.

09:25:04 17 Q. And then you went through A-2?

09:25:07 18 A. Yes.

09:25:08 19 Q. And B-1?

09:25:09 20 A. Yes.

09:25:10 21 Q. And B-2; correct?

09:25:11 22 A. Correct.

09:25:12 23 Q. And B-2, as I understood your testimony, was the one  
09:25:16 24 that ended up getting the lowest amounts of the 1-1  
09:25:19 25 impurity; is that correct?

Myerson - Cross

09:25:20 1 A. Yes.

09:25:21 2 Q. And, approximately, what were the parts per million  
09:25:24 3 on that?

09:25:24 4 A. It was from less than 2 PPM to 12 PPM.

09:25:28 5 Q. Okay. Now, you understand that we're here talking  
09:25:34 6 about Claim 3 of the '349 patent; is that right?

09:25:39 7 A. Yes.

09:25:40 8 Q. And you're testifying specifically on whether that's  
09:25:43 9 obvious or not; is that right?

09:25:44 10 A. Correct.

09:25:45 11 Q. So, here's Claim 3. You see it up there on the  
09:25:48 12 screen; is that right?

09:25:49 13 A. Yes.

09:25:51 14 Q. And it does make reference in the last paragraph, as  
09:25:54 15 you pointed out, to essentially free, which in the terms of  
09:25:59 16 the patent means 200 PPM or less; right?

09:26:02 17 A. Correct.

09:26:03 18 Q. It does not specify any particular way of  
09:26:09 19 accomplishing that -- that level of impurity; is that right?

09:26:14 20 A. In the claim itself, that's correct.

09:26:17 21 Q. And the claim itself is what we're determining for --  
09:26:21 22 looking at for obviousness; is that right?

09:26:23 23 A. Well, the claim itself looks for obviousness but of  
09:26:28 24 course a POSA interprets a claim based on the specification.  
09:26:32 25 And the specification, of course, has the synthetic process



Myerson - Cross

09:26:35 1 in it.

09:26:36 2 Q. Okay. So -- well, is it your testimony then that the

09:26:39 3 synthetic -- what is the synthetic process in this spec?

09:26:41 4 It's B-2 in this instance?

09:26:42 5 A. That's correct.

09:26:43 6 Q. Is it your testimony that to infringe this claim a

09:26:49 7 POSA would have to use B-2?

09:26:51 8 A. No.

09:26:52 9 Q. Okay. So, there is no method of controlling the

09:27:02 10 1-1 impurity specifically claimed in the patent; is that

09:27:05 11 right?

09:27:06 12 A. You mean -- oh, specific -- did you say specifically

09:27:10 13 claimed? I'm sorry.

09:27:10 14 Q. Yes, I did.

09:27:11 15 A. Yeah, not specifically in the claim. I agree with

09:27:14 16 that.

09:27:14 17 Q. Okay. And the claim -- actually, the B-2, I think

09:27:20 18 you just said was -- it was single digits, I think, for

09:27:23 19 parts per million or up to 10 perhaps?

09:27:26 20 A. It was up to 12. Less than 2 and up to 12.

09:27:29 21 Q. Okay. And so the amount that the claim calls for is

09:27:33 22 considerably higher than that as an upper limit on the

09:27:37 23 impurities; is that right?

09:27:39 24 A. Right. But of course, I think you're -- you're doing

09:27:43 25 something that happens all the time. You're talking about

Myerson - Cross

09:27:45 1 the API and the claim is to the pharmaceutical composition.

09:27:49 2 Q. Yeah. And the claim is to something considerably

09:27:52 3 higher than the level that could be accomplished with B-2;

09:27:57 4 isn't that right?

09:27:58 5 A. Again, that's right, but you're connecting something

09:28:01 6 that's not exactly the same.

09:28:03 7 Q. 200 is greater than 12; is that right, Doctor?

09:28:06 8 A. 200 is in the pharmaceutical composition and the less

09:28:09 9 than 2 to 12 is in the API. But I agree with you that the

09:28:13 10 number 200 is greater than the --

09:28:15 11 Q. Thank you.

09:28:16 12 A. -- the number 12.

09:28:17 13 Q. Thank you.

09:28:17 14 Now, also in Claim 3, Doctor, there is reference

09:28:22 15 to excipients. You talked about that; correct?

09:28:25 16 A. Correct.

09:28:25 17 Q. And in the reference to the excipients, it talks

09:28:28 18 about four categories of excipients; is that right?

09:28:32 19 A. Correct.

09:28:33 20 Q. Fillers, disintegrants, glidants and lubricants; is

09:28:36 21 that right?

09:28:36 22 A. Correct.

09:28:37 23 Q. It does not specify particular excipients; is that

09:28:42 24 right?

09:28:42 25 A. That's correct.

Myerson - Cross

09:28:43 1 Q. And -- and there are many, many fillers, for  
09:28:47 2 instance; is that right?

09:28:48 3 A. Yes.

09:28:48 4 Q. Okay. Can you give me a ballpark?

09:28:50 5 A. Not really. I mean there -- there are more common  
09:28:55 6 fillers and less common fillers. You'd have to go make a  
09:28:58 7 list and take a look.

09:28:58 8 Q. Okay. There are many, many disintegrants; is that  
09:29:01 9 right?

09:29:01 10 A. Actually, not many, many disintegrants, but I'll say  
09:29:04 11 that there are a number of different disintegrants.

09:29:06 12 Q. Okay. There are a number of different glidants; is  
09:29:09 13 that correct?

09:29:09 14 A. Again -- there are a number of different ones, yes.

09:29:13 15 Q. And there are a number of different lubricants; is  
09:29:16 16 that right?

09:29:16 17 A. A limited set of lubricants, but there are -- there  
09:29:19 18 are a number of different ones.

09:29:21 19 Q. Okay. And so for purposes of your analysis here,  
09:29:25 20 we're not talking about specific -- it's -- they don't claim  
09:29:29 21 in Claim 3 specific quantities of a particular filler; is  
09:29:34 22 that right?

09:29:34 23 A. That's correct.

09:29:35 24 Q. And they don't claim specific quantities of a  
09:29:38 25 particular filler that should be used with specific

Myerson - Cross

09:29:40 1 quantities of a particular disintegrant; is that right?

09:29:43 2 A. That's correct.

09:29:43 3 Q. And it's true for all four, they don't claim an  
09:29:47 4 entire group of those four disintegrants where a particular  
09:29:52 5 disintegrant -- or excuse me. I got a word wrong. I'll  
09:29:56 6 start again, Doctor.

09:29:57 7 They don't -- they don't claim one group of  
09:30:03 8 those four excipients that specifies every excipient and the  
09:30:07 9 amounts of those excipients; right?

09:30:08 10 A. That's correct.

09:30:10 11 Q. They leave it to the person of skill in the art to  
09:30:14 12 make that determination; right?

09:30:15 13 A. Correct.

09:30:16 14 Q. And that's something well within the level of skill  
09:30:19 15 in the art; is that right?

09:30:20 16 A. Correct. And they do have examples in the patent  
09:30:24 17 that inform a POSA.

09:30:26 18 Q. Okay. And so what's at issue here is whether it  
09:30:29 19 would be obvious to use fillers, disintegrants, glidants,  
09:30:32 20 and lubricants; is that right? That's the issue?

09:30:34 21 A. No, the issue -- actually, the issue is --

09:30:37 22 Q. Well --

09:30:37 23 A. -- the entire claim.

09:30:39 24 Q. Fair enough, Doctor. Fair enough.

09:30:41 25 But with respect to the excipient part of the

Myerson - Cross

09:30:43 1 claim --

09:30:44 2 MS. PIROZZOLO: Your Honor, can he finish his  
09:30:46 3 answer?

09:30:46 4 THE COURT: He said it's the entire claim. That  
09:30:49 5 is the obvious answer, I think he's done.

09:30:50 6 Go ahead.

09:30:51 7 MR. LOMBARDI: Okay.

09:30:56 8 BY MR. LOMBARDI:

09:30:56 9 Q. And so, Doctor, what's at issue here is would it have  
09:30:59 10 been obvious on this part of the claim -- the whole claim is  
09:31:02 11 at issue, but for this part of the claim is whether it would  
09:31:04 12 have been obvious to use these categories of excipients;  
09:31:06 13 correct?

09:31:06 14 A. You know, I -- I mean I understand what you're  
09:31:15 15 saying, I guess. Don't you do an obvious analysis looking  
09:31:19 16 at all the elements of the claim together?

09:31:22 17 So -- so, to me, it's whether they do these four  
09:31:26 18 categories to make a pharmaceutical composition of  
09:31:29 19 cabozantinib that's essentially free.

09:31:32 20 Q. Okay. Fair enough.

09:31:33 21 All right. Doctor, you -- as part of your  
09:31:36 22 obviousness analysis, we know that the Brown application --  
09:31:42 23 published application was disclosed. That's prior art;  
09:31:47 24 correct?

09:31:47 25 A. Correct.

Myerson - Cross

09:31:48 1 Q. Okay. And you talked about Brown yesterday and this  
09:31:51 2 morning; correct?

09:31:52 3 A. Correct.

09:31:53 4 Q. And you assumed for your obviousness analysis that a  
09:31:56 5 person of skill in the art would have known about the  
09:32:00 6 cabozantinib crystalline malate salt based on Brown;  
09:32:06 7 correct?

09:32:06 8 A. Yes. They would have known about the malate salt,  
09:32:08 9 that's correct.

09:32:09 10 Q. Okay. And you would have -- they would have -- you  
09:32:11 11 would have known a person of skill in the art -- you're  
09:32:14 12 assuming that a person of skill in the art would know --  
09:32:15 13 would have known that Brown teaches its use as a treatment  
09:32:19 14 for disease; is that right?

09:32:21 15 A. Yes. I believe Brown discloses that.

09:32:24 16 Q. Okay. Given that assumption -- well, let me put up  
09:32:27 17 on the screen just something to help guide our discussion.

09:32:32 18 This is --

09:32:33 19 MR. LOMBARDI: Could we put up the Doctor's  
09:32:35 20 slide PDX-4.10, please.

09:32:35 21 BY MR. LOMBARDI:

09:32:51 22 Q. Doctor, this is one of your slides -- there we go.

09:32:54 23 This is one of your slides from early in your  
09:32:57 24 testimony; is that right?

09:32:58 25 A. Yes.

Myerson - Cross

09:32:59 1 Q. And it's --

09:32:59 2 MR. LOMBARDI: Just for the record, it's PDX 4.4

09:33:02 3 and it's titled "Summary of opinions."

09:33:02 4 BY MR. LOMBARDI:

09:33:05 5 Q. Did I get that right?

09:33:06 6 A. Yes.

09:33:07 7 Q. Now, given that knowledge of the person of skill in  
09:33:12 8 the art about cabozantinib with a crystalline form and its  
09:33:16 9 use as a pharmaceutical, each of these -- there it is.

09:33:26 10 All right. Let me step back.

09:33:28 11 Each of -- you put forward on this slide four  
09:33:31 12 things that you considered discoveries that were made by  
09:33:33 13 Exelixis involving the 1-1 impurity; is that right?

09:33:37 14 A. Yes.

09:33:39 15 Q. And given knowledge that cabozantinib was out there  
09:33:45 16 known in the art and could be used for pharmaceutical  
09:33:47 17 purposes, a person of skill in the art would have been  
09:33:51 18 motivated to do each of these things; isn't that correct?

09:33:54 19 A. I'm sorry. I don't think -- I think that's -- maybe  
09:34:04 20 I'm not following the phrasing of your question, but the  
09:34:07 21 first one is --

09:34:08 22 THE COURT: So, actually, you know, can't you  
09:34:10 23 rephrase the question because I think it doesn't actually  
09:34:13 24 make any sense.

09:34:14 25 MR. LOMBARDI: Maybe I got something wrong.

Myerson - Cross

09:34:15 1 I'll try -- let me try again, Your Honor.

09:34:15 2 BY MR. LOMBARDI:

09:34:17 3 Q. So you set forth on this slide Exelixis' discoveries  
09:34:23 4 regarding the 1-1 impurity; is that right?

09:34:25 5 A. Yeah.

09:34:25 6 Q. And you talk about that Exelixis discovered the  
09:34:29 7 formation of a degradation product in the first bullet;  
09:34:33 8 right?

09:34:35 9 A. Yes. During the synthesis, right.

09:34:37 10 Q. And then discovered the degradation product when  
09:34:40 11 exposed to heat and water in the next one; is that right?

09:34:42 12 A. Right.

09:34:43 13 Q. And then they thought -- discovered that due to  
09:34:45 14 chemical interactions 1-1 could form; is that right?

09:34:49 15 A. Yes.

09:34:50 16 Q. And discovered that the 1-1 impurity is genotoxic.

09:34:55 17 Do you see that?

09:34:56 18 A. Yeah.

09:34:56 19 Q. And so my question is: Each of those discoveries --  
09:35:00 20 for each of those discoveries, a person of skill in the art  
09:35:04 21 would have been motivated to do the work that led to them;  
09:35:07 22 isn't that true?

09:35:08 23 A. Well, I think that's kind of a hindsight analysis  
09:35:12 24 because, of course, you're not motivated to know that  
09:35:16 25 something is a degradation product. When you're -- when



Myerson - Cross

09:35:19 1 you're working on development, you might discover it's a  
09:35:22 2 degradation product but that's something you're not  
09:35:26 3 motivated for. It's just -- it's just something you would  
09:35:28 4 find out when you were doing further development --

09:35:32 5 Q. Okay.

09:35:32 6 A. -- of the compound.

09:35:33 7 Q. Okay. Well, let's talk about it. Let's talk about  
09:35:35 8 the first one first, the first bullet point.

09:35:37 9 A. Yes.

09:35:38 10 Q. Doctor, it's the 1-1 could form as a degradation  
09:35:41 11 product during the synthesis of the API.

09:35:44 12 Do you see that?

09:35:44 13 A. Yes.

09:35:45 14 Q. So, we -- we're making the assumption that  
09:35:49 15 cabozantinib is out there and known; is that right?

09:35:52 16 A. Right. It's out there and known, and there's a  
09:35:57 17 process to make it in Brown.

09:35:58 18 Q. And understanding the physiochemical characteristics  
09:36:03 19 of an API is an important step in the drug development  
09:36:08 20 process; correct?

09:36:09 21 A. That's correct.

09:36:09 22 Q. In every drug development project, the team will be  
09:36:12 23 motivated to figure out what the physiochemical  
09:36:16 24 characteristics of the API are?

09:36:17 25 A. That's correct.

Myerson - Cross

09:36:18 1 Q. And in this case, that would be cabozantinib; right?

09:36:21 2 A. Correct.

09:36:22 3 Q. And it would be a normal progression in the drug  
09:36:26 4 development process for a POSA to do pre-formulation  
09:36:30 5 studies?

09:36:31 6 A. That's correct.

09:36:32 7 Q. This helps the POSA determine how to develop the  
09:36:35 8 product?

09:36:35 9 A. That's correct.

09:36:36 10 Q. And to determine suitable technologies to use the  
09:36:39 11 formulation, to use in the formulation?

09:36:41 12 A. That's correct.

09:36:43 13 Q. Now, it's important to know the degradation products  
09:36:47 14 that are made in the synthesis of an API?

09:36:51 15 A. That's correct.

09:36:52 16 Q. And a POSA would consider it important to know that?

09:36:56 17 A. Yes.

09:37:00 18 Q. And actually, a person of skill in the art would be  
09:37:05 19 very concerned about having degradation products in this  
09:37:09 20 drug that they're making because they want to make the best  
09:37:12 21 drug they can; right?

09:37:14 22 A. That's correct. Of course, there are -- when  
09:37:21 23 developing a drug and looking at degradation products, as I  
09:37:24 24 think I talked about a lot at my deposition, you're often  
09:37:30 25 looking at known impurities and unknown impurities and, in

Myerson - Cross

09:37:34 1 fact, part of the development process might be to determine  
09:37:37 2 what these unknown degradation products are.

09:37:40 3 Q. And that's something formulation scientists do all  
09:37:42 4 the time; correct?

09:37:43 5 A. You're skipping a step. We're talking about the  
09:37:47 6 synthetic people, the -- which are looking at the synthetic  
09:37:52 7 process and then separately the formulation people do  
09:37:56 8 additional work that -- that we talked about.

09:38:00 9 Q. And there are -- they're both looking for degradation  
09:38:02 10 products; correct?

09:38:03 11 A. Yeah, at different times, for different purposes, but  
09:38:06 12 yes.

09:38:06 13 Q. And actually it's not just that a person of skill in  
09:38:09 14 the art would be motivated to find these degradation  
09:38:12 15 products, the FDA requires it, doesn't it?

09:38:15 16 A. Okay. So now if we talk about that, we actually -- I  
09:38:21 17 don't think anybody put up the actual numbers of guidance  
09:38:25 18 for impurities in drug products, but typically you have to  
09:38:30 19 identify impurities that are over a thousand PPM and those  
09:38:36 20 impurities that are under a thousand PPM could be listed as  
09:38:40 21 unknown impurities unless they're determined to be -- unless  
09:38:43 22 you have a reason to think they're genotoxic or  
09:38:46 23 carcinogenic.

09:38:47 24 Q. But have you to find the impurities. The FDA tells  
09:38:50 25 you to find the impurities; is that right?

Myerson - Cross

09:38:52 1 A. No. What I just said is exactly correct. A thousand  
09:38:57 2 PPM, you have to identify what they are. Under a thousand  
09:39:01 3 PPM, they get listed as unknown impurities. And eventually  
09:39:05 4 you might determine what they are particularly if they turn  
09:39:10 5 out to be genotoxic.

09:39:12 6 Q. Okay. Let's put up -- I think you have this. It's  
09:39:15 7 DTX-274 and -- and if you want your binder -- and I can put  
09:39:20 8 it on the screen. I will put it on the screen.

09:39:22 9 A. I'm having a little trouble.

09:39:23 10 Q. With the screen? Okay.

09:39:24 11 A. I'd like to like look in the binder.

09:39:27 12 Q. Fine. DTX-274.

09:39:29 13 A. Yes. Right.

09:39:38 14 Q. Got it?

09:39:38 15 A. Yeah.

09:39:39 16 Q. Okay. Just to make sure we're on the right page,  
09:39:42 17 Doctor, it's -- what you're looking at is the guidance for  
09:39:44 18 industry Q3A impurities in new drug substances; is that  
09:39:50 19 right?

09:39:50 20 A. Actually, I was giving you the number of this that  
09:39:53 21 I -- that I just happened to know.

09:39:56 22 Q. Okay. But that's what you have in front of you;  
09:39:57 23 right?

09:39:57 24 A. Yes.

09:39:58 25 MR. LOMBARDI: Okay. Let's go to Page 3. Yes.

Myerson - Cross

09:40:07 1 There.

09:40:07 2 BY MR. LOMBARDI:

09:40:08 3 Q. And at the top it says, "Rationale for the reporting  
09:40:10 4 and control of impurities."

09:40:12 5 Do you see that, Doctor?

09:40:13 6 A. I do.

09:40:14 7 Q. And then the first sentence says, "The applicant  
09:40:19 8 should summarize the actual and potential impurities most  
09:40:22 9 likely to arise during the synthesis, purification and  
09:40:25 10 storage of a new drug substance."

09:40:28 11 Do you see that?

09:40:29 12 A. Yes.

09:40:29 13 Q. And when we're talking about a new drug substance,  
09:40:32 14 we're talking about something like cabozantinib; right?

09:40:34 15 A. Correct. Something that hasn't been approved yet.

09:40:37 16 Q. Okay. And so, a person of skill in the art would be  
09:40:42 17 motivated when they start to work with a compound that  
09:40:46 18 they've synthesized to find degradation products during the  
09:40:50 19 synthesis of the API; is that right?

09:40:52 20 A. Yes. Again, they'll see them in the HPLC. They  
09:40:57 21 won't necessarily identify what they are.

09:41:00 22 Q. Okay. And, sir, when you look at the claims in this  
09:41:04 23 case, the inventors here did not claim any new methods of  
09:41:08 24 looking for degradation products in the synthesis of the  
09:41:13 25 API; is that right?

Myerson - Cross

09:41:14 1 A. I'm sorry. Maybe --

09:41:15 2 MR. LOMBARDI: Let's -- can we put the slide

09:41:17 3 back up? PDX 4.10.

09:41:21 4 THE WITNESS: I just didn't get the question.

09:41:22 5 BY MR. LOMBARDI:

09:41:22 6 Q. I'm going to give it to you again. I think it'll

09:41:25 7 help maybe. It's at -- I'm reading from the slide, so --

09:41:26 8 A. It might help.

09:41:27 9 Q. The inventors did not claim any new methods of

09:41:31 10 looking for degradation products that could arise during the

09:41:35 11 synthesis of the API?

09:41:37 12 A. New method, no.

09:41:39 13 Q. And, in fact, the inventors said use known techniques

09:41:42 14 to do that; is that correct?

09:41:43 15 A. That's correct.

09:41:44 16 Q. And there's nothing in the patent that says that a

09:41:46 17 person of skill in the art would not have been able to

09:41:49 18 locate the degradation products; is that right?

09:41:53 19 A. That's correct.

09:41:54 20 Q. And, in fact, the presence of reaction impurities and

09:41:58 21 or processing impurities may be determined by analytical

09:42:02 22 techniques known in the art; is that right?

09:42:04 23 A. That's correct.

09:42:05 24 Q. And actually, that's -- that was a quote from Brown;

09:42:09 25 right?

Myerson - Cross

09:42:09 1 A. If you tell me it is, that's fine. But -- but I  
09:42:14 2 agree with the statement.

09:42:15 3 Q. And Brown is an Exelixis patent application; correct?

09:42:19 4 A. Yes.

09:42:21 5 Q. Yes. Okay.

09:42:22 6 MR. LOMBARDI: Let's go to the second one.

09:42:22 7 BY MR. LOMBARDI:

09:42:25 8 Q. 1-1 could form as a degra -- de -- excuse me. 1-1  
09:42:29 9 could form as a degradation product when cabozantinib  
09:42:32 10 (L)-malate was exposed to heat and water.

09:42:37 11 Do you see that?

09:42:37 12 A. Yes.

09:42:38 13 Q. That's another one of the discoveries that you talked  
09:42:40 14 about; correct?

09:42:42 15 A. Yes.

09:42:43 16 Q. Okay. And a person of skill in the art would have  
09:42:46 17 been motivated to determine what the degradation products  
09:42:51 18 would be when cabozantinib (L)-malate was exposed to heat  
09:42:55 19 and water; is that right?

09:42:59 20 A. I would agree that at some point somebody would have  
09:43:01 21 done a stress test on probably cabozantinib (L)-malate to  
09:43:04 22 look at the effects of heat and water on the API  
09:43:08 23 incompetent. Agree with that.

09:43:08 24 Q. That's routine work for formulation scientists; isn't  
09:43:11 25 that right?

Myerson - Cross

09:43:12 1 A. Actually, that's -- that's work that's done on the  
09:43:17 2 API in terms of chemical stability at some point in the  
09:43:22 3 development process. I'm not sure who's going to do it, but  
09:43:26 4 it's done.

09:43:26 5 Q. Okay. You're making a distinction between perhaps a  
09:43:30 6 chemist that does its synthesis and somebody who does the  
09:43:33 7 formulation?

09:43:33 8 A. Yeah, and sometimes there's actually a material  
09:43:36 9 science group in between.

09:43:37 10 Q. Okay. But persons of skill in the art would do it --

09:43:39 11 A. Yeah.

09:43:40 12 Q. -- is that right?

09:43:41 13 And they'd know how to do it; correct?

09:43:42 14 A. Yes.

09:43:43 15 Q. And it's another thing that the FDA requires to be  
09:43:48 16 done; isn't that right?

09:43:49 17 A. At some point in development; that's correct.

09:43:53 18 Q. Okay. And the FDA, when it's looking for degradation  
09:43:57 19 products, they're specifically looking for impurities that  
09:44:02 20 result from a chemical change in the drug substance brought  
09:44:05 21 about by the manufacture or storage of the new drug product  
09:44:10 22 by effect of light, temperature, pH, water, things like  
09:44:16 23 that; is that right?

09:44:16 24 A. Yes, because those are very important both in the  
09:44:19 25 manufacturing and the stability of the drug on the shelf.



Myerson - Cross

09:44:22 1 Q. Now, the patent doesn't claim any novel ways of  
09:44:27 2 determining a degradation product when cabozantinib  
09:44:32 3 (L)-malate was exposed to heat and water; is that correct?

09:44:36 4 A. That's correct.

09:44:42 5 Q. I'm sorry. I didn't hear you.

09:44:44 6 And what -- the patent assumes or says is that  
09:44:53 7 the POSA, the person of ordinary skill in the art could use  
09:44:56 8 known techniques to make that kind of determination; isn't  
09:45:00 9 that right?

09:45:00 10 A. Sorry. Which -- what are we talking about now?

09:45:03 11 Q. Well, the patent doesn't claim any novel ways of  
09:45:06 12 determining degradation products when cabozantinib is  
09:45:10 13 exposed to heat and water; is that right?

09:45:12 14 A. Yes, I understand that. Yeah.

09:45:13 15 Q. Okay. A POSA would use known techniques; is that  
09:45:17 16 right?

09:45:17 17 A. Known techniques to -- to look for degradation  
09:45:21 18 products, yes, I agree with that.

09:45:22 19 Q. And the patent -- and you would expect a person of  
09:45:26 20 skill in the art, it's within their skill to make a  
09:45:29 21 determination of the degradation to products when  
09:45:32 22 cabozantinib is exposed to heat and water; is that right?

09:45:35 23 A. Yes. Yes. It can be quite a bit of work, but that's  
09:45:41 24 correct.

09:45:41 25 Q. Okay. All right.

Myerson - Cross

09:45:43 1 MR. LOMBARDI: Let's go to the third one.

09:45:43 2 BY MR. LOMBARDI:

09:45:46 3 Q. 1-1 could form due to chemical interactions between  
09:45:50 4 cabozantinib (L)-malate and certain excipients. That is the  
09:45:55 5 third of the discoveries on your chart; is that right?

09:45:57 6 A. Correct.

09:45:58 7 Q. Now, we talked about preformulation. What this  
09:46:04 8 describes -- or let me strike the question and start again,  
09:46:10 9 Doctor.

09:46:10 10 Determining the chemical interactions between a  
09:46:15 11 active ingredient and excipients is part of what we've  
09:46:20 12 talked about being preformulation; right?

09:46:22 13 A. That's correct. It's -- we've heard this described  
09:46:25 14 as excipient compatibility studies, which is what it's  
09:46:28 15 usually described as.

09:46:29 16 Q. Okay. And these excipient compatibility studies is  
09:46:33 17 part of the normal process of pharmaceutical development;  
09:46:36 18 correct?

09:46:36 19 A. Yes. In this case, this is formulation development;  
09:46:40 20 correct.

09:46:40 21 Q. One of the first things you do when you're -- I've  
09:46:43 22 got the right scientists now. It's formulators now; right?

09:46:46 23 A. Right.

09:46:47 24 Q. And one of the first things you do as a formulator is  
09:46:51 25 excipient compatibility studies; right?

Myerson - Cross

09:46:53 1 A. Yes.

09:46:55 2 Q. This is what formulators do day in and day out; is  
09:46:58 3 that right?

09:46:58 4 A. Every time they have a new API, they do excipient  
09:47:03 5 compatibility studies. I agree with that.

09:47:05 6 Q. And then the person of skill in the art determines  
09:47:07 7 which excipients are necessary; is that right?

09:47:10 8 A. After they do the excipient compatibility studies and  
09:47:16 9 they have determined a dose and a type of drug product, they  
09:47:20 10 then start selecting individual excipients to make -- to  
09:47:26 11 make trial formulations.

09:47:28 12 Q. Okay. And you determined which excipients will be  
09:47:35 13 compatible with a particular API; is that right?

09:47:40 14 The formulation scientists?

09:47:41 15 A. That's correct. You're looking, of course, to  
09:47:43 16 minimize any decomposition.

09:47:46 17 Q. Okay. Ultimately, a POSA knows that you want to use  
09:47:50 18 only the excipients that are physically and chemically  
09:47:54 19 compatible with the API; is that right?

09:47:57 20 A. Right. That's the first step. Yes.

09:47:59 21 Q. Okay. And that's something that persons of skill in  
09:48:02 22 the art are well qualified to do?

09:48:05 23 A. I agree with that.

09:48:07 24 Q. The patent doesn't claim any novel ways of  
09:48:11 25 determining whether there's a chemical interaction between

Myerson - Cross

09:48:14 1 cabozantinib and the excipients used; is that right?

09:48:19 2 A. That's correct.

09:48:21 3 Q. It's done using known methods; correct?

09:48:25 4 A. I'm sorry?

09:48:29 5 Q. Let me -- that was not a great question. Let me ask  
09:48:32 6 that again.

09:48:33 7 The patent suggests just using known methods to  
09:48:36 8 make that kind of determination; isn't that right?

09:48:38 9 A. I don't actually remember the passage related to  
09:48:42 10 that, so we'd have to see it. But it wouldn't surprise me.

09:48:45 11 Q. Okay. That's consistent with your understanding as  
09:48:47 12 an expert in this field; is that right?

09:48:50 13 A. (Witness nods head.) Yes.

09:48:51 14 Q. Now, let's go to the last one, the discovery that the  
09:48:54 15 1-1 impurity is genotoxic, do you see that one?

09:48:57 16 A. Yes.

09:48:58 17 Q. Okay. Now, a person of skill in the art would have  
09:49:01 18 been motivated to determine whether any of the impurities in  
09:49:06 19 the compound -- in the composition are genotoxic; correct?

09:49:11 20 A. Yes. And at somewhere in the development process,  
09:49:17 21 that would be the case.

09:49:18 22 Q. Okay. A POSA would have wanted to control for  
09:49:23 23 genotoxic impurities in a formulation; right?

09:49:26 24 A. Yes. Generally you wish to control within certain  
09:49:30 25 limits on genotoxic impurities.

Myerson - Cross

09:49:33 1 Q. Okay. And genotoxic impurities, I mean, just so --  
09:49:38 2 genotoxic is -- refers to testing that has shown that  
09:49:42 3 something can cause the chromosomal makeup of cells; isn't  
09:49:48 4 that right?

09:49:48 5 A. It -- well, it's -- a genotoxic impurity is something  
09:49:53 6 that will interact with DNA. And the initial test, of  
09:49:59 7 course, is a bacterial test called the Ames test.

09:50:02 8 Q. Okay. All right. But the idea is that you're  
09:50:06 9 concerned with the genotoxic impurity -- if something is  
09:50:09 10 genotoxic, it can harm DNA; is that right?

09:50:12 11 A. Yes; potentially harm DNA in people, though not  
09:50:15 12 always.

09:50:16 13 Q. Yeah, not always. But you do laboratory tests on  
09:50:19 14 this?

09:50:19 15 A. That's right.

09:50:20 16 Q. And genotoxic impurity can cause genetic or  
09:50:23 17 chromosomal damages -- damage. And some of those, some  
09:50:27 18 could be carcinogenic; is that right?

09:50:29 19 A. That's correct.

09:50:30 20 Q. And that's why a POSA is particularly interested in  
09:50:33 21 making the determination whether impurities are genotoxic;  
09:50:36 22 is that right?

09:50:37 23 A. That's correct.

09:50:38 24 Q. Now, a genotoxic impurity is particularly concerning,  
09:50:45 25 isn't it?

Myerson - Cross

09:50:46 1 A. Yes.

09:50:48 2 Q. Because, in the worst case, it could show that  
09:50:51 3 something's carcinogenic; right?

09:50:53 4 A. Correct.

09:50:54 5 Q. And so when a genotoxic impurity is identified,  
09:51:00 6 additional investigation is always warranted?

09:51:04 7 A. Yes.

09:51:06 8 Q. And the conservative approach, Doctor, is to assess  
09:51:09 9 known genotoxic compounds as potential carcinogens, unless  
09:51:14 10 there's experimental evidence to the contrary; is that  
09:51:17 11 right?

09:51:17 12 A. Yes.

09:51:18 13 Q. And obviously -- I mean, a person of skill in the art  
09:51:22 14 is obviously going to make determinations of whether  
09:51:28 15 impurities are genotoxic; that's within the level of skill  
09:51:31 16 in the art, isn't it?

09:51:33 17 A. Well, they, of course, will look for structures that  
09:51:38 18 they think are concerning and then determine if they're  
09:51:40 19 genotoxic. That is correct.

09:51:42 20 Q. Okay. That's -- that is what a person of skill in  
09:51:44 21 the art would do, look for structures they think are  
09:51:47 22 concerning?

09:51:47 23 A. At some point in the development process, that's  
09:51:49 24 correct.

09:51:50 25 Q. All right. And are -- is that -- your reference to

Myerson - Cross

09:51:53 1 structures that are concerning, is that also sometimes  
09:51:56 2 called structural alerts?

09:51:57 3 A. That's right.

09:51:58 4 Q. Okay. And these structural alerts are known in the  
09:52:02 5 art; is that right?

09:52:03 6 A. Right.

09:52:05 7 Q. And you can use structural alerts which you then have  
09:52:11 8 to test out experimentally, but you can use structural  
09:52:14 9 alerts to give you an indication about what the nature of  
09:52:17 10 the impurity is you're dealing with; is that correct?

09:52:20 11 A. Well, I would -- I would phrase it this way: Use  
09:52:23 12 structural alerts to identify compounds that you're going to  
09:52:30 13 further test via the Ames test, do an experimental test to  
09:52:33 14 determine genotoxicity.

09:52:35 15 Q. Okay. They're called alerting structures or  
09:52:40 16 structure alerts because they're intended to give an alert  
09:52:43 17 that there might be genotoxicity?

09:52:45 18 A. That's right.

09:52:46 19 Q. Okay. And these structural alerts are actually  
09:52:50 20 pretty accurate in predicting whether you'll get  
09:52:53 21 genotoxicity, not 100 percent but they're pretty accurate?

09:52:56 22 A. I would -- I would kind of differ -- maybe we're  
09:52:59 23 differing about what "pretty accurate" means.

09:53:00 24 Q. How about 70 percent of the time?

09:53:02 25 A. Yeah, that's -- yes. 65, 70 percent of the time.

Myerson - Cross

09:53:06 1 Q. Okay. And then, the next step, if the structural  
09:53:11 2 alerts give you some indication, is to do an Ames test?

09:53:15 3 A. That's right. In fact, always -- always follow  
09:53:19 4 through with the Ames test.

09:53:20 5 Q. And that's what a person of skill in the art would  
09:53:22 6 do, is always follow through with an Ames test; is that  
09:53:24 7 right?

09:53:25 8 A. That's right.

09:53:25 9 Q. And when you follow through with the Ames test, you  
09:53:27 10 make a determination whether an impurity is genotoxic; is  
09:53:30 11 that right?

09:53:31 12 A. Right. If it's positive on the AMES test, it -- it  
09:53:33 13 at least appears to be genotoxic.

09:53:36 14 Q. Okay. And with respect to the regulators, regulators  
09:53:44 15 expect to be told about whether an impurity is genotoxic or  
09:53:49 16 not; is that right?

09:53:50 17 A. That's correct.

09:53:51 18 Q. And when the -- when an impurity is genotoxic, then  
09:53:58 19 you take steps in the way you formulate the product; is that  
09:54:04 20 right?

09:54:04 21 A. You take steps in controlling the level of that  
09:54:10 22 impurity in the formulated product and on storage.

09:54:14 23 Q. Okay. Now, a POSA would have known that cabozantinib  
09:54:21 24 was potentially genotoxic based on structural alerts; is  
09:54:25 25 that right?



Myerson - Cross

09:54:26 1 A. Right. Yeah. The quinoline, so you would have --  
09:54:29 2 you would have checked. But that's right.

09:54:31 3 Q. Okay. So, that's -- you got one step ahead of me,  
09:54:35 4 but 1-1 is something called a quinoline; correct?

09:54:40 5 A. Right. I mean, cabozantinib is a quinoline. 1-1's a  
09:54:43 6 quinoline. And we're talking about a lot of quinoline  
09:54:46 7 structures here.

09:54:47 8 Q. Okay. And a quinoline structure is a kind of  
09:54:49 9 chemical structure?

09:54:50 10 A. That's right.

09:54:51 11 Q. And it's a kind of chemical structure that you find  
09:54:54 12 in cabozantinib?

09:54:55 13 A. Yes.

09:54:56 14 Q. And it's in 1-1?

09:54:57 15 A. Yes.

09:54:58 16 Q. And -- and that is a red flag for a person of skill  
09:55:02 17 in the art?

09:55:03 18 A. It's -- it's -- it's a structure that has to be  
09:55:09 19 furtherly -- further evaluated. Because, of course, as we  
09:55:13 20 know, there are lots of quinolines that are actually drugs.  
09:55:17 21 And there are quinolines that are -- that are genotoxic. So  
09:55:22 22 you have to -- you have to say -- you have to study each  
09:55:24 23 particular quinoline to determine whether it's useful, not  
09:55:29 24 harmful or harmful.

09:55:31 25 Q. So, to a person of skill in the art, determining that

Myerson - Cross

09:55:35 1 something's a quinoline, which they could tell -- let me

09:55:38 2 just ask you this first: You can tell if something's a

09:55:40 3 quinoline or not by looking at the chemical structure?

09:55:43 4 A. That's right.

09:55:44 5 Q. The drawing on the page. Somebody of skill in the

09:55:46 6 art could say, "That is or is not a quinoline based on that

09:55:51 7 structure"?

09:55:51 8 A. That's correct.

09:55:52 9 Q. And when something is a quinoline, you actually --

09:55:55 10 that is a structural alert right there; isn't that right?

09:55:58 11 A. That's correct.

09:56:00 12 Q. So, a person of skill in the art would then take the

09:56:02 13 quinoline and put it in the Ames test; is that right?

09:56:05 14 A. Yes, again, at some point, that's correct.

09:56:08 15 Q. Yeah. And the Ames test is -- it's A-M-E-S; correct?

09:56:12 16 Named after a person; isn't that right?

09:56:15 17 A. That's right.

09:56:15 18 Q. Bruce Ames; right?

09:56:16 19 A. Right.

09:56:17 20 Q. And the Ames test is -- it's really one of the most

09:56:20 21 famous tests out there, isn't it?

09:56:23 22 A. That's right.

09:56:24 23 Q. It's widely used?

09:56:25 24 A. Yes.

09:56:26 25 Q. Persons of skill in the art know how to use the Ames

Myerson - Cross

09:56:29 1 test?

09:56:29 2 A. Yes.

09:56:29 3 Q. Persons of skill in the art use the Ames test  
09:56:32 4 routinely?

09:56:33 5 A. Yes, I would agree with that.

09:56:35 6 Q. And persons of skill in the art understand the  
09:56:38 7 results they get from an Ames test; is that right?

09:56:40 8 A. Yes.

09:56:43 9 Q. Okay. And a person of skill in the art, who had the  
09:56:47 10 1-1 impurity, would determine -- first they determine that  
09:56:52 11 the API was potentially genotoxic based on the quinoline  
09:56:58 12 structure; isn't that right?

09:56:59 13 A. You mean the cabozantinib?

09:57:00 14 Q. Cabozantinib, I'm sorry. Did I say -- let me give  
09:57:03 15 you another -- thank you. I'll give you another question.  
09:57:05 16 I apologize.

09:57:06 17 Person of skill in the art would -- would look  
09:57:11 18 at the structure for the 1-1 impurity and say, "That's  
09:57:15 19 potentially genotoxic because it's a quinoline"?

09:57:19 20 A. Yes.

09:57:22 21 Q. And then they would do the Ames test?

09:57:24 22 A. Yes.

09:57:26 23 Q. And then they would find out in the Ames test that  
09:57:28 24 it's positive?

09:57:29 25 A. Yes.

Myerson - Cross

09:57:30 1 Q. And then they would know that, in their formulation,  
09:57:34 2 they need to do what they can to minimize that component?

09:57:38 3 A. That's correct.

09:57:41 4 Q. Okay. Now, there's no claim made in the patent as to  
09:57:46 5 a novel way of determining genotoxicity; right?

09:57:50 6 A. Correct.

09:57:51 7 Q. You can use known techniques?

09:57:52 8 A. Correct.

09:57:56 9 Q. There's nothing claimed in the patent that's -- that  
09:58:01 10 claims a novel way of determining that there's been --  
09:58:06 11 there's an impurity that is genotoxic; is that right?

09:58:10 12 A. Could you repeat that?

09:58:13 13 Q. I'm sorry. I think I'm repeating myself, so I'll  
09:58:16 14 just move on, Doctor.

09:58:17 15 Let me move to another subject here -- well,  
09:58:40 16 actually, Doctor, while we're here lets -- you talked about  
09:58:43 17 the pharmaceutical composition.

09:58:47 18 MR. LOMBARDI: If you could just put the  
09:58:49 19 Doctor's demonstrative PDX-4.15 up.

09:58:49 20 BY MR. LOMBARDI:

09:58:58 21 Q. And, Doctor, I'm just focused, for the moment, on the  
09:59:02 22 top one there. The essentially free limitation applies to  
09:59:07 23 the pharmaceutical composition; is that right?

09:59:10 24 A. Correct.

09:59:11 25 Q. Okay. And your testimony was that it's not just the

Myerson - Cross

09:59:16 1 API that has to be essentially free of the impurity. It's  
09:59:20 2 the entire pharmaceutical composition?

09:59:23 3 A. That's correct.

09:59:23 4 Q. Which would include the excipients; correct?

09:59:28 5 A. Pharmaceutical composition is the final drug product,  
09:59:33 6 which includes the API plus all excipients.

09:59:36 7 Q. Okay. And the patent doesn't claim any novel way of  
09:59:42 8 coming up with a composition that controls for those  
09:59:47 9 impurities; is that right?

09:59:49 10 A. Other than disclosing a synthetic process that makes  
09:59:54 11 an API exceptionally low, it doesn't then have an  
09:59:59 12 additional -- anything additional that would control for the  
10:00:03 13 1-1.

10:00:04 14 Q. And what the -- what the patent actually says is as a  
10:00:08 15 matter of composition, people should use -- persons of skill  
10:00:13 16 in the art should use known techniques; is that right?

10:00:15 17 A. I'm sorry, composition of?

10:00:17 18 Q. Pharmaceutical composition. The pharmaceutical  
10:00:20 19 composition in this case, they should use known techniques?

10:00:23 20 A. I'm sorry. Known techniques to determine the  
10:00:27 21 pharmaceutical composition, is that...

10:00:28 22 Q. To make it, yes. To make the pharmaceutical  
10:00:30 23 composition.

10:00:30 24 A. Yes, that's correct.

10:00:32 25 MR. LOMBARDI: Okay. And if we look at the

Myerson - Cross

10:00:34 1 '349 patent, which is JTX-4, again. Column 20, please.

10:00:47 2 THE WITNESS: What is that in your binder or...

10:00:47 3 BY MR. LOMBARDI:

10:00:51 4 Q. JTX-4. It's just the patent.

10:00:54 5 A. Yeah, I'm just -- I'm --

10:00:55 6 Q. In my binder, it should be -- it's around the middle  
10:00:59 7 of the binder I'm told.

10:01:00 8 A. I got it.

10:01:01 9 Q. Okay. And tell me when you're to Column 20, Doctor.

10:01:10 10 A. Yes, I'm there.

10:01:11 11 Q. Okay. And do you see there's a heading about halfway  
10:01:14 12 down that says "Pharmaceutical compositions"; is that right?

10:01:17 13 A. Yes.

10:01:18 14 MR. LOMBARDI: And at Line 40, if we could  
10:01:21 15 highlight that.

10:01:21 16 BY MR. LOMBARDI:

10:01:22 17 Q. You see the patent says, "Various carriers used" --  
10:01:27 18 first of all, it's under the heading "Pharmaceutical  
10:01:29 19 compositions"; right?

10:01:30 20 A. Correct.

10:01:31 21 Q. It says, "Various carriers used in formulating  
10:01:34 22 pharmaceutically acceptable compositions and known  
10:01:37 23 techniques for their bulk preparation and subsequent  
10:01:41 24 production into unit dosage forms are employed to make the  
10:01:46 25 pharmaceutical compositions disclosed herein."

Myerson - Cross

10:01:49 1 Do you see that?

10:01:50 2 A. Yes.

10:01:50 3 Q. That's what the patent says?

10:01:52 4 A. Correct.

10:01:53 5 Q. And it specifically cites to a couple of sources.

10:01:56 6 Remington is a very well-known source; is that  
10:01:59 7 right?

10:01:59 8 A. Correct.

10:01:59 9 Q. And Swarbrick is as well; is that right?

10:02:01 10 A. Correct.

10:02:02 11 Q. On Column 21, if you go down to Line 37, it talks --  
10:02:13 12 it's talking -- tell me when you have it, Doctor.

10:02:15 13 A. Yes.

10:02:16 14 Q. Okay. You see this is the paragraph that begins "in  
10:02:19 15 another aspect."

10:02:21 16 Do you see that?

10:02:22 17 A. In another embodiment, yes.

10:02:25 18 Q. I'm reading from where it says "in another aspect."  
10:02:29 19 I just want to make sure we're in the same place.

10:02:31 20 A. Column 21 you said?

10:02:33 21 Q. Column 21, Line 37.

10:02:37 22 A. Oh, 37, yes. "In another aspect," yes.

10:02:40 23 Q. Got it. Okay.

10:02:41 24 It says, "In another aspect, the disclosure  
10:02:44 25 provides a pharmaceutical composition according to" various

Myerson - Cross

10:02:47 1 tables.

10:02:48 2 Do you see that?

10:02:48 3 A. Yes.

10:02:49 4 Q. "The compositions are prepared according to methods  
10:02:53 5 available to the skilled artisan."

10:02:55 6 Do you see that?

10:02:56 7 A. Yes.

10:02:57 8 Q. "For example, the tablet formulations are prepared by  
10:03:00 9 combining, blending, and compacting the components of the  
10:03:04 10 tablet compositions."

10:03:07 11 Do you see that?

10:03:07 12 A. Yes.

10:03:09 13 Q. "The capsule compositions are prepared by combining  
10:03:11 14 and blending the components and then placing the blend in a  
10:03:15 15 gelatin capsule."

10:03:16 16 Do you see that?

10:03:17 17 A. Yes.

10:03:18 18 Q. And so, the patent is -- well, let me go to one more  
10:03:22 19 spot.

10:03:22 20 MR. LOMBARDI: Column 30, please.

10:03:22 21 BY MR. LOMBARDI:

10:03:28 22 Q. Tell me when you've got that, Doctor.

10:03:30 23 A. Yes.

10:03:30 24 Q. All right. At the very bottom -- the bottom  
10:03:33 25 paragraph under the heading "Stability studies."



Myerson - Cross

10:03:37 1 MR. LOMBARDI: A little bit farther down. There  
10:03:39 2 you go.

10:03:39 3 BY MR. LOMBARDI:

10:03:39 4 Q. "Stability studies of pharmaceutical compositions."

10:03:42 5 Do you see that?

10:03:42 6 A. Yes.

10:03:43 7 Q. "The pharmaceutical capsule composition of Tables 3  
10:03:46 8 and 4 were prepared by mixing the ingredients according to  
10:03:49 9 processes known in the art."

10:03:51 10 Do you see that?

10:03:53 11 A. Yes.

10:03:54 12 Q. So, what the patent says in those places is that it's  
10:03:57 13 up to the person of skill in the art to do those kinds of  
10:04:00 14 tasks; isn't that right?

10:04:02 15 A. Yes.

10:04:04 16 Q. Okay. All right. Now, I'm ready to move to  
10:04:08 17 something else, Doctor. Get a couple things out of the way  
10:04:16 18 here.

10:04:17 19 Let me go to, again, one of your slides, just to  
10:04:29 20 make sure we're in the right place.

10:04:32 21 MR. LOMBARDI: It's the slide number PDX-4.15,  
10:04:38 22 please.

10:04:38 23 BY MR. LOMBARDI:

10:04:41 24 Q. And the second part of this slide, Doctor, you talked  
10:04:46 25 about inherency; correct?

Myerson - Cross

10:04:48 1 A. Yes.

10:04:50 2 Q. All right. And we've had a lot of discussion about  
10:04:51 3 inherency, both in your testimony and others; is that right?

10:04:55 4 A. Correct.

10:04:57 5 Q. Okay. And so I want to talk a little bit about  
10:04:59 6 inherency. You talked in A about Brown Example 1 allowing  
10:05:06 7 for variation. And I think it was in that context that you  
10:05:09 8 put up PTX-35. And I'm going to --

10:05:15 9 MR. LOMBARDI: Let me put it up on the screen,  
10:05:16 10 so you can see exactly what we're talking about.

10:05:16 11 BY MR. LOMBARDI:

10:05:19 12 Q. Do you remember this document, PTX-0035?

10:05:21 13 And it should be in your binder if you prefer to  
10:05:24 14 look at that, whichever may way you prefer to do it.

10:05:27 15 A. Okay. I do remember the document.

10:05:28 16 Q. Okay. While you're looking, can you tell us what the  
10:05:30 17 document is?

10:05:31 18 A. Yes. This is the Exelixis' NDA discussing  
10:05:39 19 manufacturing processes.

10:05:43 20 Q. Okay. An Exelixis doc -- and you -- an Exelixis  
10:05:46 21 document and you used this on your direct examination;  
10:05:49 22 correct?

10:05:49 23 A. That's correct.

10:05:51 24 MR. LOMBARDI: And I want to turn to -- Page 16,  
10:05:55 25 I believe, is specifically where you looked. There was a

Myerson - Cross

10:05:59 1 table there called Table 2.

10:06:01 2 THE WITNESS: Yes.

10:06:01 3 BY MR. LOMBARDI:

10:06:02 4 Q. And you were looking -- these are those four  
10:06:06 5 processes that you described for us in detail yesterday?

10:06:09 6 A. Yes.

10:06:11 7 Q. And you highlighted across A-2 because that was Brown  
10:06:18 8 Example 1; right?

10:06:18 9 A. Correct.

10:06:19 10 Q. And you noted --

10:06:23 11 MR. LOMBARDI: Why don't we go ahead and  
10:06:24 12 highlight across there just so we're tracking what you did  
10:06:27 13 before.

10:06:27 14 BY MR. LOMBARDI:

10:06:27 15 Q. And you noted that there is a column for the 1 to  
10:06:33 16 1 -- I said 1 to 1 -- it's the 1-1 impurity; is that right?

10:06:37 17 A. Yes.

10:06:38 18 Q. And in that column, it shows a range of impurities.

10:06:42 19 Do you see that?

10:06:43 20 A. Yes.

10:06:44 21 Q. Which you pointed out; correct?

10:06:47 22 A. Correct.

10:06:48 23 Q. And the range is 35 to 411 parts per million;  
10:06:53 24 correct?

10:06:53 25 A. Correct.

Myerson - Cross

10:06:54 1 Q. And you pointed out that 411 is above 200; correct?

10:06:58 2 A. Correct.

10:06:59 3 Q. Now, there's nothing on this document that says what  
10:07:05 4 lot is being tested there or what lots are being tested  
10:07:10 5 there; is there?

10:07:13 6 A. Not -- not in this table, that is correct.

10:07:16 7 Q. Okay. And have you seen the underlying data for  
10:07:22 8 this?

10:07:22 9 A. I've seen lots of underlying data and this has to be  
10:07:27 10 using the GTI specific method. And the reason I say that is  
10:07:31 11 because the old methods could not get a number under 200.

10:07:36 12 Q. Okay.

10:07:36 13 A. So -- so, I have seen tables for the GTI specific  
10:07:41 14 methods, but the numbers are slightly different from the  
10:07:44 15 numbers reported in this table.

10:07:47 16 Q. Okay. Well, I guess what I'm referring to is you  
10:07:53 17 don't -- have you seen the lab notebooks where the result  
10:07:56 18 say the 411 result was received?

10:07:59 19 Have you seen those lab notebooks?

10:08:01 20 A. I've seen -- again, I've seen -- I think it was put  
10:08:09 21 up in Court already. I've seen a document that had the --  
10:08:16 22 result for the GTI specific method for four batches and it  
10:08:21 23 included numbers that were consistent with these, but not  
10:08:24 24 exactly the same.

10:08:25 25 Q. Okay. But -- so that's my question.

Myerson - Cross

10:08:28 1 A. Yeah.

10:08:28 2 Q. I'm talking about the number -- I want to know what  
10:08:32 3 the underlying documents are for the 411 and you can't help  
10:08:36 4 me with that; is that right?

10:08:37 5 A. I -- I don't believe -- I mean, if we could look at  
10:08:41 6 that GTI specific test result that was put up in Court  
10:08:46 7 before, I'm not sure -- I don't think it was 411. It was --  
10:08:51 8 it was over 200, but I don't remember what it was. But  
10:08:54 9 that's the only document that I've seen that has the GTI  
10:08:59 10 specific results for A-2 batches.

10:09:06 11 Q. Okay. So this document doesn't tell us, for  
10:09:11 12 instance -- it doesn't say on the face of the document what  
10:09:14 13 the method was that was used for that -- what the method was  
10:09:19 14 to make that particular lot; correct?

10:09:25 15 A. I'm sorry. It says it's the A-2 method.

10:09:27 16 Q. The A-2 method. It doesn't say -- it doesn't say who  
10:09:31 17 made the lots?

10:09:32 18 A. That's correct.

10:09:33 19 Q. So, it doesn't say whether it was Regis, for  
10:09:36 20 instance?

10:09:36 21 A. That's correct.

10:09:38 22 Q. It doesn't say whether it was -- do you say Girindus  
10:09:41 23 or Girindus?

10:09:42 24 A. I've been saying Girindus.

10:09:44 25 Q. Girindus. So I think --

Myerson - Cross

10:09:45 1 A. Whatever you prefer.

10:09:46 2 Q. Yeah, I think we're on the same page. So I'll call  
10:09:48 3 it Girindus.

10:09:49 4 So it doesn't say whether it's Girindus?

10:09:51 5 A. That's correct.

10:09:53 6 Q. We would need to see more documents to understand  
10:09:57 7 what the testing is that's being referred to here; correct?

10:10:00 8 A. Again, we do have the little A next to the results  
10:10:09 9 there that say the GTI -- that it used GTI testing. And so,  
10:10:15 10 the only documents we have are a result that show GTI  
10:10:20 11 testing and we'd have to match those and see how they line  
10:10:23 12 up.

10:10:23 13 Q. But what we're interested here -- what you testified  
10:10:27 14 about was whether Brown, the Brown example inherently  
10:10:34 15 produces essentially -- impurity essentially -- composition  
10:10:39 16 essentially free of an impurity; is that right?

10:10:41 17 A. That's correct.

10:10:43 18 Q. And we can't tell from this, what's here, what the  
10:10:47 19 method of manufacture was?

10:10:48 20 A. No. I think you're misspeaking again. We know it's  
10:10:53 21 the A-2 process. We don't know which -- which entity  
10:11:02 22 manufactured it, but we know it was manufactured by the A-2.

10:11:05 23 We know two things looking at this and it's very  
10:11:07 24 clear. We know it's made by the A-2 process and we know it  
10:11:10 25 was tested by the GTI specific method. And because of that,

Myerson - Cross

10:11:15 1 we know, actually by looking at another document,  
10:11:20 2 that whether it's 35 to 411 PPM or 34 to 350 PPM, we know at  
10:11:28 3 least one batch is above 200 PPM.

10:11:31 4 Q. Okay. So, just to close this out, and I think  
10:11:37 5 maybe -- you can keep that up for one more second. Got it?  
10:11:46 6 Okay.

10:11:47 7 I just want to make sure we're clear because we  
10:11:50 8 went back and forth a little bit on that. We don't know who  
10:11:54 9 manufactured these lots?

10:11:55 10 A. It doesn't -- okay. I'm going to -- I'm going to  
10:12:01 11 phrase that slightly differently. It doesn't say who  
10:12:03 12 manufactured these lots. But as far as I know, in all the  
10:12:07 13 documents we've seen, the only four lots manufactured by the  
10:12:11 14 A-2 process, that were submitted to the FDA, were the three  
10:12:17 15 Regis batches and the one Girindus batch.

10:12:18 16 Q. It would help if we had the underlying lab notebooks  
10:12:22 17 for this; right?

10:12:22 18 A. It would be useful, yes.

10:12:24 19 Q. Okay. Thank you.

10:12:25 20 So, sir, let me -- you mentioned Girindus, and I  
10:12:31 21 think -- well, let me put up a document you had.

10:12:36 22 MR. LOMBARDI: PTX-38, please.

10:12:36 23 BY MR. LOMBARDI:

10:12:43 24 Q. And that one, it's in -- it might be easier from your  
10:12:46 25 direct binder, it's Tab 11.

Myerson - Cross

10:12:48 1 A. Okay.

10:12:49 2 Q. For you to find that.

10:13:01 3 Tell me when you've got it.

10:13:03 4 A. Okay. I do.

10:13:04 5 Q. All right. And I believe it's the second page? The  
10:13:09 6 second page, I believe, was the chart you were looking at,  
10:13:13 7 Doctor.

10:13:14 8 Does that look familiar?

10:13:15 9 A. Yes. That's -- that's the chart that makes use of  
10:13:22 10 one -- of the older -- one of the older HPLC methods, but  
10:13:25 11 that's correct.

10:13:26 12 Q. Okay. And just so that we are all back on the same  
10:13:31 13 page, what you looked at was -- there's a -- below there,  
10:13:37 14 just a little bit lower, for the 1-1 impurity.

10:13:41 15 Do you see that? And I'll try to highlight it.

10:13:43 16 There you go. Right there.

10:13:44 17 That's one of the things you highlighted; right,  
10:13:47 18 Doctor?

10:13:47 19 A. Correct.

10:13:48 20 Q. All right. And then you noted that -- that tells you  
10:13:54 21 how much of the 1-1 impurity is detected; right?

10:13:58 22 A. Well, in this particular method, it tells you if it  
10:14:02 23 was -- if it was above or below 200 PPM, because that's the  
10:14:07 24 limit of detection of this particular test.

10:14:08 25 Q. Fair enough. And if it's ND, then it's below 200?



Myerson - Cross

10:14:13 1 A. Correct.

10:14:14 2 Q. All right. And you noted in the far right column,  
10:14:19 3 that's the Girindus lot; that right?

10:14:24 4 A. Correct.

10:14:25 5 Q. And the Girindus lot had something above 200;  
10:14:30 6 correct?

10:14:30 7 A. Correct.

10:14:31 8 Q. And the .06 translates to 600 parts per million; is  
10:14:35 9 that right?

10:14:36 10 A. Correct.

10:14:37 11 Q. And you said, you pointed out, well look, it's --  
10:14:40 12 it's also got a difference in total impurities, do you see  
10:14:44 13 that?

10:14:45 14 A. Yes.

10:14:45 15 Q. And you said the total impurities -- you were  
10:14:48 16 pointing down at the bottom, at the 0.36; is that right?

10:14:52 17 A. Correct.

10:14:52 18 Q. Now, so, Girindus comes out differently than Regis;  
10:14:58 19 is that right?

10:14:59 20 A. It's actually purer than Regis.

10:15:02 21 Q. Okay. And Regis used exactly the method of example  
10:15:09 22 two; is that right?

10:15:10 23 A. Well, when you say "exactly," what you mean is they  
10:15:15 24 followed Example 2 of the -- of Brown. But, of course, in  
10:15:22 25 any long synthetic process, there's always variability. So,

Myerson - Cross

10:15:27 1 they followed Brown within the variability of Brown.

10:15:33 2 Q. The language used by Exelixis in its IND to describe  
10:15:38 3 how the clinical material was manufactured is identical to  
10:15:43 4 Example 1 Brown; is that right?

10:15:45 5 A. That's right. But Example 1 of Brown, as we've  
10:15:48 6 heard, says the word about 27 times, which means it's  
10:15:52 7 variable. In fact, all synthetic processes are variable.

10:15:56 8 Q. Yeah, well -- right. So, sir, about that, the word  
10:16:00 9 -- it's actually the word "approximately."

10:16:01 10 A. I'm sorry, I should have said "approximately."

10:16:03 11 Q. And you didn't express any opinion on approximately  
10:16:06 12 before in this case; right?

10:16:08 13 A. I didn't express an opinion about approximately in  
10:16:13 14 the example, that's true. Though, I did quote from other  
10:16:16 15 parts of the patent. And I also, in my deposition, noted  
10:16:19 16 that synthetic processes vary from batch to batch.

10:16:25 17 Q. Yeah. You have didn't testify about the word  
10:16:26 18 "approximately," did you?

10:16:27 19 A. I would agree with that.

10:16:28 20 Q. Okay. So this is the first you're talking about  
10:16:31 21 approximately?

10:16:31 22 A. Yes. But I've actually sat in the courtroom and  
10:16:34 23 heard testimony about the term "approximately."

10:16:37 24 Q. And -- and did you know that the word "approximately"  
10:16:40 25 is used in the '394 patent?

Myerson - Cross

10:16:45 1 A. In the 39 -- in the '394 patent, probably. I would  
10:16:50 2 expect it is used.

10:16:51 3 Q. '349, I'm sorry.

10:16:53 4 A. '349.

10:16:54 5 And it goes to the fact that synthetic processes  
10:16:57 6 are never exactly the same when done every time. There's  
10:17:02 7 always variability in a synthetic process.

10:17:06 8 Q. Well, for something --

10:17:06 9 A. And we don't have a batch record. You know, no one  
10:17:12 10 has actually discussed this in this case. But the reason,  
10:17:15 11 when you manufacture a batch, you have something called a  
10:17:18 12 batch record, is it has -- it has a procedure. And then  
10:17:23 13 next to it somebody has to write in pen what the actual  
10:17:27 14 conditions were.

10:17:28 15 And so, it says, you know, heat to 70 degrees.  
10:17:31 16 And it might say we heat it to 68 degrees. Right. And so  
10:17:36 17 that's how -- that's how synthetic processes are done.  
10:17:40 18 Unfortunately, we've never seen a batch record for any of  
10:17:42 19 these.

10:17:46 20 Q. That's -- Exelixis would have those; right?

10:17:48 21 A. I've never seen a batch record for any of the four  
10:17:51 22 processes.

10:17:51 23 Q. Okay. Now, "approximately" is used all the time in  
10:17:55 24 pharmaceutical -- in pharmaceutical formulations; correct?

10:17:59 25 That -- that term is used frequently?

Myerson - Cross

10:18:01 1 A. I think we're talking about synthetic processes, not  
10:18:04 2 formulations.

10:18:05 3 Q. Okay. Fair enough.

10:18:06 4 A. And it's used all the time.

10:18:08 5 Q. Yeah. And it's used when the quantities in question  
10:18:11 6 do not have to be precise; is that right?

10:18:14 7 A. Its quantities, its temperature, and its time.

10:18:18 8 Q. Right. Correct. And they use it when those -- those  
10:18:22 9 parameters don't have to be precise; is that right?

10:18:25 10 A. They use it to say you want to be in this range, but  
10:18:31 11 they don't have to be exactly the same.

10:18:33 12 Q. Right. Because there are other places where precise  
10:18:37 13 quantities are used; isn't that right?

10:18:39 14 A. There are places where the word "approximately"  
10:18:44 15 doesn't appear, and it will say something very precise, I  
10:18:47 16 agree with that.

10:18:48 17 Q. Right. So the -- and you know that's the case for  
10:18:52 18 the Brown formulation, too, for the -- for Example 1 of  
10:18:56 19 Brown; isn't that right?

10:18:57 20 A. Yeah. Again, you're using the word "formulation."

10:18:59 21 Q. I apologize. I apologize. I'll start again so that  
10:19:02 22 you can get a clean question.

10:19:04 23 A. Yeah.

10:19:05 24 Q. In Brown, Example 1, the word "approximately" is not  
10:19:09 25 used with respect to all quantities; is that right?

Myerson - Cross

10:19:12 1 A. That's correct.

10:19:14 2 Q. Okay. In fact, precise numbers are used with some of  
10:19:19 3 the quantities; is that right?

10:19:21 4 A. That's correct.

10:19:22 5 Q. Now, you agree that the Regis process -- well, the  
10:19:31 6 Regis process and Girindus got different results in this  
10:19:35 7 Table 1 that you put up; is that right?

10:19:37 8 A. I mean, they -- they have different amounts of the  
10:19:43 9 1-1 impurity, certainly, that we talked about. And the  
10:19:47 10 overall purity is different, meaning that the Girindus is  
10:19:52 11 purer than the -- than the three Regis batches.

10:19:55 12 Q. Okay. So, the Girindus 1-1 is, what, it's at least  
10:20:02 13 three times as much, at least three times as much as what's  
10:20:06 14 detected in the Regis batches; is that right?

10:20:09 15 A. Yeah, using -- using this HPLC method, of course, we  
10:20:14 16 actually have more accurate data on this, using the GTI  
10:20:19 17 method. And so your -- your multiplier would be better than  
10:20:23 18 three, you know, if we looked at that, but they're certainly  
10:20:26 19 different.

10:20:26 20 Q. Okay. Well, I'm just using your exhibit; right?

10:20:29 21 A. Right.

10:20:29 22 Q. And your exhibit, you said --

10:20:31 23 A. Yeah.

10:20:32 24 Q. -- that there's more for Girindus than for the Regis;  
10:20:35 25 is that right?

Myerson - Cross

10:20:36 1 A. That's correct.

10:20:37 2 Q. And it's over 200. And it's 600; is that right?

10:20:42 3 A. In -- in this method, yes. It says 600.

10:20:45 4 Q. Okay. There were no deviations in the Regis process  
10:20:53 5 from Example 1 in Brown; is that right?

10:20:56 6 A. I don't believe that's what it says in the document.  
10:21:00 7 I've seen a document at some point that does say there were  
10:21:06 8 deviations. And, actually, Dr. Lepore was cross-examined  
10:21:09 9 about that and was shown a document that was up in Court  
10:21:14 10 that said there were deviations.

10:21:16 11 Q. Sir, it's correct that the Regis process does not  
10:21:19 12 include deviations from Example I of Brown; correct?

10:21:23 13 A. You're quoting my deposition because I hadn't seen  
10:21:27 14 that document before. But, of course, I've been sitting in  
10:21:29 15 court and I get to watch what goes on, and there is a  
10:21:32 16 document that says there are deviations, so that's a factual  
10:21:36 17 statement.

10:21:36 18 You know, I can't not know what I saw in Court.  
10:21:39 19 So, if you want to impeach me with what I said in my  
10:21:43 20 deposition, that's fine. But I learned something in Court,  
10:21:45 21 which I'm aloud to talk about.

10:21:46 22 Q. Okay. Well, I think you handled it for me, which is,  
10:21:48 23 you testified at your deposition differently than you're  
10:21:52 24 testifying today --

10:21:52 25 A. Right.

Myerson - Cross

10:21:53 1 Q. -- on that point; is that right?

10:21:54 2 A. Right, because I saw something with -- it's a factual  
10:21:57 3 statement that was brought out in Court that I saw, and it  
10:22:00 4 does say that.

10:22:01 5 Q. Okay. You admit that there are deviations in the  
10:22:05 6 Girindus process, deviations from Brown Example 1?

10:22:09 7 A. Sure.

10:22:09 8 Q. And there are a number of things called planned  
10:22:14 9 deviations in Girindus; is that right?

10:22:16 10 A. That's correct.

10:22:17 11 Q. And I don't think we have to go through them all, but  
10:22:20 12 you're aware that Dr. Lepore, during his testimony, went  
10:22:26 13 through and pulled out some of those -- or all of those  
10:22:29 14 deviations; is that right?

10:22:30 15 A. That's correct.

10:22:31 16 Q. And -- and you don't disagree with the things he  
10:22:34 17 pulled out that were called planned deviations; is that  
10:22:37 18 right?

10:22:37 19 A. Yes, they're clearly listed in the Girindus document  
10:22:40 20 as planned deviation. And they are deviations.

10:22:43 21 Q. Okay. And so, we have planned deviations in Girindus  
10:22:47 22 from the Brown Example 1 method; is that right?

10:22:50 23 A. That's correct.

10:22:51 24 Q. And when we do those planned -- we test that batch  
10:22:56 25 with the planned deviations, we get different results; is

Myerson - Cross

10:23:00 1 that right?

10:23:01 2 A. The results are different, I agree with that.

10:23:03 3 Q. And the results are well above the 200 parts per  
10:23:07 4 million; is that right?

10:23:08 5 A. Correct.

10:23:09 6 Q. And there's a difference in the overall purity; is  
10:23:13 7 that correct?

10:23:13 8 A. Correct.

10:23:25 9 Q. And I think I just have one other thing for you,  
10:23:29 10 Doctor. Just one moment. Just a couple of questions.

10:23:44 11 MR. LOMBARDI: And we can take that down now.

10:23:44 12 BY MR. LOMBARDI:

10:23:46 13 Q. You gave some testimony about crystallization and  
10:23:50 14 recrystallization; is that right?

10:23:53 15 A. Yes.

10:23:53 16 Q. And you talked about -- you've talked about  
10:23:56 17 crystallization and recrystallization in your reports; is  
10:23:59 18 that right?

10:24:00 19 A. Yes.

10:24:00 20 Q. And you talked about it in your testimony; is that  
10:24:02 21 right?

10:24:02 22 A. Yes.

10:24:03 23 Q. And crystallization is recommended by the FDA; is  
10:24:09 24 that right?

10:24:09 25 A. That's right.



Myerson - Cross

10:24:11 1 Q. For all impurities at or above .1 percent; is that  
10:24:15 2 right?

10:24:16 3 A. I'm -- I -- I -- it's recommended -- it's recommended  
10:24:23 4 as a final purification step irregardless if they're below  
10:24:27 5 or above 1 percent. It's actually usually the final  
10:24:31 6 purification step in the manufacture of any API purification  
10:24:35 7 step.

10:24:35 8 Q. And you -- there's a -- are you familiar with the  
10:24:38 9 Robinson reference you cited in your expert report?

10:24:41 10 A. Yes.

10:24:41 11 Q. Okay. And in the Robinson reference, you saw that it  
10:24:47 12 says, "Conventional processes such as fractional  
10:24:51 13 crystallization and recrystallization can be used"; is that  
10:24:54 14 right?

10:24:55 15 A. Correct.

10:24:55 16 Q. And you agree that those are conventional processes;  
10:24:59 17 is that right?

10:24:59 18 A. That's correct.

10:25:00 19 Q. And actually one method for dealing -- you said in  
10:25:03 20 your report, one method for dealing with removing genotoxic  
10:25:08 21 impurities is recrystallization; correct?

10:25:10 22 A. There's always something that you're -- that you're  
10:25:13 23 interested in doing, but, of course, as I noted, it doesn't  
10:25:17 24 always work.

10:25:17 25 Q. Okay. As a general rule, crystallization will

Myerson - Redirect

10:25:21 1 improve purity; is that right?

10:25:23 2 A. As a general rule, it will -- it will improve  
10:25:29 3 overall -- overall purity, but won't necessarily improve the  
10:25:36 4 purity of each individual component if there are multiple  
10:25:40 5 impurities.

10:25:40 6 Q. Is it true that more often than not in your  
10:25:43 7 experience crystallization improves the overall purity of a  
10:25:47 8 material?

10:25:47 9 A. Oh, yeah. Generally it will improve the overall  
10:25:50 10 impurity, but, again, might have problem with the specific  
10:25:53 11 impurity.

10:25:54 12 Q. A person of skill in the art would have known how to  
10:25:57 13 perform crystallization; is that right?

10:26:00 14 A. Certainly.

10:26:00 15 Q. And they would have known how to perform  
10:26:03 16 recrystallization?

10:26:03 17 A. Yes.

10:26:04 18 Q. And the patents don't claim a novel method of  
10:26:08 19 recrystallization; is that right?

10:26:09 20 A. Correct.

10:26:10 21 Q. And they don't claim a novel method of  
10:26:12 22 crystallization; is that right?

10:26:13 23 A. Correct.

10:26:14 24 Q. Okay.

10:26:14 25 MR. LOMBARDI: No further questions, Your Honor.

Myerson - Redirect

10:26:16 1 THE COURT: All right. So, I think we need to  
10:26:18 2 take our morning break here. So we'll take a 15-minute  
10:26:21 3 break.

10:26:21 4 THE CLERK: All rise.

10:26:27 5 (Recess was taken.)

10:43:45 6 DEPUTY CLERK: All rise.

10:43:46 7 THE COURT: All right. Redirect.

10:43:47 8 Everyone be seated.

10:43:48 9 MS. PIROZZOLO: Thank you, Your Honor.

10:43:49 10 REDIRECT EXAMINATION

10:43:49 11 BY MS. PIROZZOLO:

10:43:49 12 Q. Could we pull up Plaintiff's Exhibit 38, which is  
10:43:53 13 Tab 11, Dr. Myerson?

10:43:57 14 MS. PIROZZOLO: And go to the page with Table 1.

10:44:01 15 A. Yes.

10:44:02 16 Q. Now, you were asked questions about Table 1; correct?

10:44:05 17 A. Yes.

10:44:07 18 Q. Now, focusing on the columns for the Regis batches,  
10:44:14 19 let's go to the line on total impurities.

10:44:17 20 Do total impurities vary among the different  
10:44:21 21 Regis batches?

10:44:22 22 A. Yes. They vary significantly between 0.87 percent to  
10:44:29 23 0.54 percent.

10:44:30 24 Q. Why would that occur if Regis was using the same A-2  
10:44:34 25 process?

Myerson - Redirect

10:44:35 1 A. Again, they're always -- they're -- there's always  
10:44:39 2 variations in synthetic processes so you never get exactly  
10:44:42 3 the same purity or impurity profile when going through any  
10:44:47 4 five-step synthetic process.

10:44:50 5 Q. Did the invention of the '349 patent include solving  
10:44:54 6 the problem of the genotoxic impurity identified by  
10:44:59 7 Exelixis?

10:44:59 8 A. It did.

10:45:00 9 Q. How did Exelixis solve that problem?

10:45:02 10 A. By developing the B-2 process, that consistently made  
10:45:09 11 cabozantinib (L)-malate with exceptionally low levels of a  
10:45:14 12 1-1 impurity from below 2 to 12 parts per million.

10:45:18 13 Q. And the B-2 process is the process described in the  
10:45:21 14 '349 patent?

10:45:21 15 A. Correct.

10:45:23 16 Q. Have you seen any evidence that adding a  
10:45:27 17 recrystallization step to the Brown process would have  
10:45:30 18 resulted in the claimed purity levels for cabozantinib  
10:45:33 19 (L)-malate?

10:45:33 20 A. No.

10:45:36 21 MS. PIROZZOLO: No further questions.

10:45:38 22 THE COURT: All right. Dr. Myerson, thank you.  
10:45:40 23 You may step down. Watch your step.

10:45:43 24 MS. PIROZZOLO: May I move for the admission of  
10:45:46 25 Plaintiff's Exhibit 773, Plaintiff's Exhibit 38, PTX-299,

Koleng - Direct

10:45:53 1 PTX-494, and Joint Exhibit 8.

10:45:58 2 MR. LOMBARDI: No objection. Your Honor.

10:45:59 3 THE COURT: All right. Admitted without  
10:46:01 4 objection.

10:46:01 5 (PTX Exhibit Nos. 773, 38, 299, and 494 were  
10:46:01 6 admitted into evidence.)

10:46:44 7 (JTX Exhibit No. 8 was admitted into evidence.)

10:46:44 8 THE COURT: Dr. Koleng, you're still sworn, all  
10:46:47 9 right.

10:46:47 10 THE WITNESS: Yes, sir.

10:46:49 11 MR. YURKERWICH: May it please the Court, Kevin  
10:46:53 12 Yurkerwich on behalf of Exelixis.

10:46:53 13 DIRECT EXAMINATION

10:46:55 14 BY MR. YURKERWICH:

10:46:55 15 Q. Good morning, Dr. Koleng.

10:46:59 16 A. Good morning.

10:46:59 17 Q. You testified earlier in the trial on the issue of  
10:47:02 18 infringement of the '349 patent; correct?

10:47:04 19 A. Correct.

10:47:05 20 Q. What patents will you address today?

10:47:06 21 A. The crystalline (L)-malate salt patents.

10:47:10 22 MR. YURKERWICH: Can we pull up PDX-5.2, please?

10:47:10 23 BY MR. YURKERWICH:

10:47:13 24 Q. What is the relationship between these patents?

10:47:16 25 A. They share a common specification and priority date.

Koleng - Direct

10:47:19 1 Q. What is that priority date?

10:47:21 2 A. As highlighted here, January 16, 2009.

10:47:26 3 Q. At a very high level, can you remind us of your  
10:47:30 4 experience with formulation development?

10:47:31 5 A. Yes, I'm a pharmaceutical scientist that's  
10:47:34 6 responsible for working with drug substances and drug  
10:47:38 7 products to create useable drug products.

10:47:41 8 Q. And what is the -- just stepping back a moment, what  
10:47:44 9 is the relationship between these three patents?

10:47:45 10 A. Again, they all relate to the crystalline (L)-malate.  
10:47:49 11 They share a common specification.

10:47:51 12 Q. Do you have -- and turning to your experience for a  
10:47:53 13 moment, do you have experience with poorly water soluble  
10:47:56 14 compounds?

10:47:56 15 A. Yes.

10:47:57 16 Q. What is your experience?

10:47:58 17 A. Most of my career has actually been addressing  
10:48:02 18 performance issues associated with what would be called  
10:48:06 19 poorly soluble drugs.

10:48:07 20 Q. What experience do you have with the preparation of  
10:48:09 21 pharmaceutical salts?

10:48:10 22 A. I've executed programs throughout my career where we  
10:48:14 23 have evaluated possible salt formation as one way to address  
10:48:19 24 problems with a drug substance.

10:48:21 25 Q. Do you have any experience with salt screening?

Koleng - Direct

10:48:23 1 A. Yes, I do.

10:48:24 2 Q. Could you tell us about your experience?

10:48:25 3 A. I have executed -- salt screen, first, is a broad  
10:48:30 4 term encompassing a large set of experimentation where we --  
10:48:35 5 in cases where we were interested in pursuing a potential  
10:48:38 6 salt, we would utilize a salt screen type of experiment as a  
10:48:43 7 first step on the road to potentially selecting one, if  
10:48:47 8 available.

10:48:48 9 Q. How many compounds have you tested in services?

10:48:50 10 A. Ten.

10:48:51 11 Q. Have you ever consulted for a pharmaceutical company  
10:48:55 12 for the purpose of identifying the best salt for a  
10:48:58 13 particular drug?

10:48:58 14 A. Yes.

10:49:00 15 MR. YURKERWICH: Let's turn to PDX-5.3, please.

10:49:00 16 BY MR. YURKERWICH:

10:49:04 17 Q. Looking at the slide, what opinions will you offer  
10:49:08 18 here today?

10:49:08 19 A. The preparation of pharmaceutical salts is  
10:49:11 20 unpredictable, that the (L)-malic acid would not have been  
10:49:15 21 selected for cabozantinib as a counterion and that  
10:49:19 22 identifying a suitable pharmaceutical salt for development  
10:49:22 23 depends upon a wide range of considerations.

10:49:25 24 Q. Are you offering an ultimate opinion on validity with  
10:49:27 25 respect to any of the asserted patents?

Koleng - Direct

10:49:29 1 A. No, sir.

10:49:30 2 MR. YURKERWICH: Can we turn to PDX-5.4?

10:49:30 3 BY MR. YURKERWICH:

10:49:34 4 Q. What is shown here?

10:49:35 5 A. These are the definitions of a person of ordinary  
10:49:38 6 skill in the art proffered by Exelixis and MSN in this case.

10:49:42 7 Q. Which definition did you apply?

10:49:44 8 A. Exelixis'.

10:49:45 9 Q. At the time of the invention, would you have  
10:49:49 10 qualified as a person of skill in the art under either of  
10:49:51 11 the definitions?

10:49:52 12 A. Yes.

10:49:54 13 Q. Would your opinions change depending on which  
10:49:56 14 definition was applied?

10:49:57 15 A. No.

10:49:59 16 Q. Let's introduce the concepts you'll be addressing  
10:50:02 17 very briefly. What is a drug substance?

10:50:04 18 A. At the highest level we've heard it's the active  
10:50:07 19 pharmaceutical ingredient, API. It's the active -- it's the  
10:50:10 20 chemical that is attributed with the therapeutic activity.

10:50:15 21 Q. Dr. Steed discussed salt screening. Is salt  
10:50:18 22 screening the only approach to formulating low solubility  
10:50:21 23 compounds?

10:50:21 24 A. No.

10:50:22 25 Q. What other approaches are there?



Koleng - Direct

10:50:23 1 A. There's a host of other approaches, including things  
10:50:26 2 like nanomilling, micronization, lipid base formulation  
10:50:31 3 approaches, solid amorphous dispersion, cyclodextrin  
10:50:36 4 complexation, among others.

10:50:37 5 Q. Were those techniques known in 2009?

10:50:39 6 A. Yes.

10:50:40 7 Q. Could those techniques have been used to formulate  
10:50:42 8 low solubility compounds?

10:50:43 9 A. Yes.

10:50:46 10 Q. What experience do you have with those techniques?

10:50:48 11 A. I've used them continuously and continue to do so  
10:50:51 12 throughout my career.

10:50:53 13 Q. How would a skilled artisan have evaluated which of  
10:50:57 14 those techniques to pursue?

10:50:58 15 A. Well, they would have had to take a holistic approach  
10:51:01 16 in assessing one, what problem they were trying to solve.  
10:51:04 17 And then, with an eye toward potential limitations  
10:51:10 18 associated with the starting materials, as well as taking  
10:51:13 19 into consideration the requirements of the entire product  
10:51:17 20 development program.

10:51:18 21 MR. YURKERWICH: Now, if we turn to PDX-5.5.

10:51:18 22 BY MR. YURKERWICH:

10:51:22 23 Q. Can you describe for the Court how a salt is formed?

10:51:25 24 A. Sure. We've seen this slide several times already.  
10:51:29 25 It's the reaction between an acid and a base.

Koleng - Direct

10:51:32 1 Q. And remind us, what is a salt screen?

10:51:35 2 A. A salt screen generally is a general term for a set  
10:51:38 3 of -- a set of experiments with very specific conditions and  
10:51:42 4 considerations that is used to evaluate if a salt can be  
10:51:46 5 formed. And if formed, what, if any, physical properties  
10:51:50 6 that material may have.

10:51:52 7 Q. Now, is a salt -- is every salt screen carried out  
10:51:55 8 the same way?

10:51:55 9 A. No.

10:52:04 10 Q. How many counterions are typically tested in a salt  
10:52:07 11 screen?

10:52:07 12 A. There's no defined number. But I would say you -- it  
10:52:12 13 could be as -- be as many as a few up to several. My  
10:52:17 14 experience has been it could be, like I said, a couple up to  
10:52:21 15 maybe 10 to 20.

10:52:23 16 MR. YURKERWICH: Now, if we turn to PDX-5.6.

10:52:23 17 BY MR. YURKERWICH:

10:52:26 18 Q. Can you -- can we talk about salt formation and how  
10:52:30 19 that can be impacted by different variables?

10:52:33 20 Can you describe what's on the slide?

10:52:35 21 A. These are all variables that have to go in that are  
10:52:38 22 all considered when performing what's been termed a salt  
10:52:41 23 screen.

10:52:42 24 Q. Directing your attention to the top left, how does  
10:52:45 25 the active ingredient affect salt formation?

Koleng - Direct

10:52:50 1 A. This is quite key. The first assessment a POSA has  
10:52:53 2 to do is to have a reasonable assessment of whether or not  
10:52:55 3 the compound will even form a salt. And if it -- if it has  
10:52:58 4 functionality that may support salt selection or salt  
10:53:02 5 formation, then they have to assess whether or not that's an  
10:53:05 6 acid or a base, for instance. An assessment or an idea of  
10:53:10 7 chemical liability, say stability is also a key -- is also a  
10:53:12 8 key here.

10:53:14 9 Q. Now, over the course of the trial we've heard the  
10:53:17 10 term  $pK_a$ . Could you describe what a  $pK_a$  is at a very high  
10:53:21 11 level?

10:53:21 12 A. Generally, it's a numeric number given to an acid  
10:53:25 13 that allows you to compare whether or not it's a relatively  
10:53:29 14 weak or strong acid.

10:53:31 15 Q. Do you recall Dr. Steed's testimony that differences  
10:53:33 16 in  $pK_a$  can impact salt section?

10:53:37 17 A. Yes.

10:53:38 18 Q. What's your response to that testimony?

10:53:40 19 A. It's only one of many factors that need to be  
10:53:42 20 considered in salt selection.

10:53:44 21 Q. In 2009, could a skilled artisan have predicted  
10:53:48 22 whether a salt formation would occur based on the  
10:53:51 23 differences between the  $pK_a$ , the counterion, and the active  
10:53:54 24 ingredient?

10:53:54 25 A. No.

Koleng - Direct

10:53:56 1 Q. What are the reasons for your opinion?

10:53:57 2 A. First that, again, the -- the differences are only  
10:54:02 3 one consideration. The other is then looking at all the  
10:54:05 4 different considerations here, including the specific  
10:54:09 5 attributes of the starting material.

10:54:11 6 Q. Now, in 2009, could a person of skill in the art have  
10:54:15 7 predicted the properties of any salt that was produced based  
10:54:18 8 on the differences between the  $pK_a$ , the counterion, and the  
10:54:21 9 active ingredient?

10:54:22 10 A. Not at all.

10:54:25 11 Q. Let's turn our attention to solvents.

10:54:28 12 How does the solvent affect salt formation?

10:54:30 13 A. So the solvents are quite key in a salt screen.  
10:54:35 14 First, the reaction that we just discussed is typically  
10:54:37 15 conducted in solution. So there's a requirement that the  
10:54:39 16 starting material be in solution, as well as the  
10:54:42 17 corresponding counterion. The choice of solvent will also  
10:54:48 18 drive whether, you know, can affect certain properties of  
10:54:50 19 the materials as well. And it also, as we've learned  
10:54:54 20 through testimony, that the choice of salts can impact the  
10:54:58 21 characteristics of whatever solid material you may  
10:55:01 22 ultimately recover.

10:55:02 23 MR. YURKERWICH: Can I direct your attention to  
10:55:05 24 Tab 2 in your binder, where you'll find PTX-0087?

10:55:10 25 BY MR. YURKERWICH:

Koleng - Direct

10:55:10 1 Q. Would you please identify this document?

10:55:13 2 A. This is the Pharmorphix report, I believe it's been  
10:55:18 3 shared previously, on the salt screen for EXEL-7184.

10:55:23 4 MR. YURKERWICH: Can we turn to Page 6 where  
10:55:25 5 you'll find Table 2 of this document?

10:55:25 6 BY MR. YURKERWICH:

10:55:26 7 Q. What is the name of Table 2?

10:55:28 8 A. "Solvents used in solvent screen."

10:55:32 9 Q. And what information is provided in Table 2?

10:55:34 10 A. So these are -- this is first, it provides a list of  
10:55:38 11 solvents that were evaluated to assess the solubility of the  
10:55:43 12 cabozantinib free base and it also -- and it has a row --  
10:55:47 13 column with the Xs and checkmarks where they've determined  
10:55:51 14 whether or not those solvents exhibited suitable solubility  
10:55:54 15 to continue with the salt -- with this experiment.

10:55:56 16 Q. Would a person of ordinary skill in the art have been  
10:55:59 17 familiar with the solvents here in Table 2?

10:56:00 18 A. Yes.

10:56:03 19 Q. Do all the solvents in Table 2 share the same  
10:56:06 20 properties?

10:56:06 21 A. Not at all.

10:56:07 22 Q. How do the properties vary among the solvents?

10:56:10 23 A. They vary widely in properties, such as melting  
10:56:13 24 point, boiling point, dielectric constant, densities among  
10:56:16 25 others, admissibility with each other for instance.

Koleng - Direct

10:56:19 1 Q. How many solvents were tested in Table 2?

10:56:28 2 A. I believe 27.

10:56:29 3 Q. And focusing on the column with results, how many  
10:56:33 4 solvents were deemed acceptable?

10:56:34 5 A. Just two, THF, tetrahydrofuran and acetone.

10:56:39 6 Q. What were the results of the other solvents?

10:56:41 7 A. They were deemed not -- not suitable or providing  
10:56:44 8 sufficient solubility.

10:56:45 9 Q. In 2009, how many solvents were available for a  
10:56:49 10 skilled artisan to have used in a salt formation experiment?

10:56:53 11 A. I think the list could be two times this, maybe  
10:56:58 12 three.

10:56:59 13 Q. Could a skilled artisan have formed a reasonable  
10:57:01 14 expectation in advance as to which, if any, of the solvents  
10:57:05 15 tested would have been successful?

10:57:06 16 A. No. That's why we do this work.

10:57:08 17 MR. YURKERWICH: Now, if we turn back to the  
10:57:10 18 demonstratives about salt formation.

10:57:10 19 BY MR. YURKERWICH:

10:57:14 20 Q. Can you discuss experimental conditions and how  
10:57:17 21 experimental conditions can -- can affect salt formation?

10:57:21 22 A. Of course. Experimental conditions, first, I'll --  
10:57:25 23 well, they typically include things like determining the  
10:57:27 24 concentration of the materials to use, the temperatures at  
10:57:31 25 which the reactions are run, whether or not the samples are

Koleng - Direct

10:57:36 1 agitated, for instance, and say how long they're -- they're  
10:57:38 2 reacted.

10:57:39 3 Q. And how, if at all, does an experimental procedure  
10:57:43 4 and the conditions used affect whether a salt will form or  
10:57:46 5 not?

10:57:46 6 A. They can directly impact it. They can either -- they  
10:57:49 7 can inhibit it, facilitate it, or -- and potentially change  
10:57:53 8 the outcome.

10:57:55 9 Q. What expectations, if any, would a skilled artisan  
10:57:57 10 have had regarding the conditions necessary for salt  
10:58:01 11 formation?

10:58:01 12 A. They wouldn't have had an expectation. They would  
10:58:04 13 have had to have started with something and then made  
10:58:07 14 adjustments through the experimentation.

10:58:10 15 Q. Do you agree with Dr. Steed's testimony that salt  
10:58:14 16 screening involves routine experimentation?

10:58:15 17 A. No, I do not.

10:58:17 18 Q. What are the reasons you disagree?

10:58:18 19 A. As we just discussed, salt screening is a very  
10:58:22 20 generic term that describes a very complex and  
10:58:24 21 individualized set of experiments for a given API.

10:58:27 22 Q. Can you give us an example from your own experience  
10:58:29 23 where a salt -- a salt screen led to unpredictable and  
10:58:33 24 unexpected results?

10:58:34 25 A. Of course. We were working with one client on three

Koleng - Direct

10:58:37 1 structurally related compounds where we were asked to  
10:58:41 2 consider salt screening as part of development.

10:58:45 3 We actually did this work at Pharmorphix, as  
10:58:48 4 well. We chose -- we did a very similar assessment. We  
10:58:53 5 chose about, I think, 15 or 16 counterions per active  
10:58:57 6 ingredient. We executed the study for two of the three. We  
10:59:03 7 actually nominated the free form or the starting form  
10:59:05 8 because it -- the salts that were formed didn't have any  
10:59:09 9 better properties. And for the third, it was only one of  
10:59:13 10 two that formed and it showed some beneficial properties  
10:59:16 11 that was nominated for progression.

10:59:18 12 Q. Were the results of your salt screening experiments  
10:59:21 13 consistent?

10:59:21 14 A. No.

10:59:22 15 Q. Were they predictable?

10:59:23 16 A. No.

10:59:25 17 MR. YURKERWICH: Turning to PDX 5.8.

10:59:25 18 BY MR. YURKERWICH:

10:59:28 19 Q. At a high level, can you describe what's on the  
10:59:32 20 screen and why a person of skill in the art -- well, can you  
10:59:37 21 describe what's on the screen?

10:59:38 22 A. Yeah. So this is a -- this stems from my second  
10:59:41 23 point that malic acid would not have been selected as a  
10:59:45 24 counterion and that's based on three reasons. First, that  
10:59:47 25 malic acid was -- is a weak acid. There are hierarchical



Koleng - Direct

10:59:51 1 approaches that favor stronger, more commonly used acids  
10:59:55 2 that a POSA would understand. And, again, malic acid  
10:59:58 3 stemming from that is a rarely used acid.

11:00:02 4 Q. Now, before we dig into your opinions here, can we  
11:00:06 5 step back and take a moment to talk about the properties of  
11:00:09 6 cabozantinib.

11:00:10 7 MR. YURKERWICH: Can we pull up PDX-5.9?

11:00:10 8 BY MR. YURKERWICH:

11:00:14 9 Q. What is shown here?

11:00:15 10 A. This is the chemical structure of cabozantinib base.

11:00:19 11 Q. In 2009, would a skilled artisan have known the  
11:00:23 12 aqueous solubility of cabozantinib based on this structure?

11:00:27 13 A. No.

11:00:27 14 Q. Was there any information in the prior art indicating  
11:00:31 15 that there were any concerns about the solubility of  
11:00:33 16 cabozantinib?

11:00:33 17 A. No.

11:00:35 18 Q. What, if any, information about cabozantinib's  $pK_a$   
11:00:38 19 was disclosed in the prior art?

11:00:40 20 A. None.

11:00:42 21 MR. YURKERWICH: Turning to the next  
11:00:43 22 demonstrative, PDX 5.10.

11:00:43 23 BY MR. YURKERWICH:

11:00:46 24 Q. In 2009, what, if any, information would a skilled  
11:00:49 25 artisan have been able to understand about whether

Koleng - Direct

11:00:52 1 cabozantinib was an acid or a base based on its structure?

11:00:55 2 A. As I discussed previously, a POSA would look at the  
11:00:59 3 structure to look for certain functional groups. They would  
11:01:03 4 identify the clinical group that's highlighted in blue and  
11:01:06 5 recognize that it was basic.

11:01:09 6 Q. Now that we've talked about the properties of  
11:01:14 7 cabozantinib, let's turn back to the opinions on your  
11:01:17 8 earlier demonstrative.

11:01:20 9 MR. YURKERWICH: And I'd like to turn our  
11:01:21 10 attention to PDX-5.11.

11:01:21 11 BY MR. YURKERWICH:

11:01:24 12 Q. What is your first reason why a skilled artisan would  
11:01:26 13 not have been motivated to pursue malic acid?

11:01:28 14 A. Malic acid is a weak acid.

11:01:32 15 MR. YURKERWICH: If you turn in your materials  
11:01:33 16 to Tab 3.

11:01:33 17 BY MR. YURKERWICH:

11:01:38 18 Q. Let me know when you're there.

11:01:40 19 A. I'm there.

11:01:41 20 Q. Could you identify the document marked as PTX-373?

11:01:45 21 A. Yes. This is the *CRC Handbook of Chemistry and*  
11:01:49 22 *Physics*, edited by David Lide.

11:01:53 23 MR. YURKERWICH: Would you turn in this exhibit  
11:01:54 24 to Page 6.

11:01:54 25 BY MR. YURKERWICH:

Koleng - Direct

11:02:02 1 Q. Could you describe the table of information beginning  
11:02:05 2 at Page 6?

11:02:06 3 A. Yeah. This is a reference on dissociation constants  
11:02:09 4 of organic acids and bases.

11:02:12 5 MR. YURKERWICH: Now, turning to Page 13.

11:02:12 6 BY MR. YURKERWICH:

11:02:14 7 Q. I'd like to direct your attention to the third row of  
11:02:17 8 the left-hand column.

11:02:24 9 A. I'm there.

11:02:25 10 Q. Do you see the reference to quinoline?

11:02:27 11 A. I do.

11:02:27 12 Q. What is the  $pK_a$  of a quinoline?

11:02:30 13 A. As shown here, 4.90.

11:02:35 14 Q. What does that tell you about a quinoline?

11:02:36 15 A. That it's a weak base.

11:02:41 16 MR. YURKERWICH: Now, I'd like to direct your  
11:02:42 17 attention to the bottom right of Page 7 in this exhibit.

11:02:48 18 And it will be, I think, eight lines from the bottom.

11:02:48 19 BY MR. YURKERWICH:

11:02:52 20 Q. Do you find malic acid?

11:02:56 21 A. Yes.

11:02:57 22 Q. What is the relevant  $pK_a$  of malic acid?

11:03:00 23 A. The relevant  $pK_a$  is 3.40.

11:03:05 24 Q. What would that have indicated to the skilled artisan  
11:03:08 25 about malic acid?

Koleng - Direct

11:03:08 1 A. That it's a weak acid.

11:03:11 2 Q. Do you recall Dr. Steed's testimony about the  
11:03:13 3 Rule-of-2?

11:03:14 4 A. Yes.

11:03:16 5 Q. Were you aware of the Rule-of-2 before this case?

11:03:18 6 A. I was generally aware of rules related to -- or  
11:03:23 7 recommendations related to differences in  $pK_a$  values. I was  
11:03:28 8 generally aware of differences of two to three or more in  
11:03:32 9 looking at counterions.

11:03:34 10 Q. Now, if we pull up from the Lide reference, the  
11:03:38 11 entries for malic acid and quinoline, in view of the  $pK_a$   
11:03:45 12 information for malic acid and quinoline, what, if anything,  
11:03:49 13 would the Rule-of-2 have told a POSA about whether or not to  
11:03:52 14 pursue a malic salt of a quinoline-containing compound?

11:03:56 15 A. Based upon the information available to a POSA in the  
11:03:59 16 literature, it would not have satisfied at least the  
11:04:02 17 Rule-of-2.

11:04:02 18 Q. Now, does the combination of malic acid and  
11:04:05 19 cabozantinib ultimately satisfy the Rule-of-2?

11:04:07 20 A. That's my understanding, yes.

11:04:09 21 Q. Could that have been reasonably expected beforehand?

11:04:12 22 A. No.

11:04:13 23 Q. Does a less than two  $pK_a$  unit difference mean that a  
11:04:16 24 salt will not form?

11:04:17 25 A. No.

Koleng - Direct

11:04:17 1 Q. Does a greater than two  $pK_a$  unit difference mean that  
11:04:20 2 a salt will form?

11:04:21 3 A. No.

11:04:24 4 Q. Turning to PDX 5.12. What is your second reason why  
11:04:29 5 a person of skill in the art would not have been motivated  
11:04:32 6 to select malic acid in a salt screen?

11:04:34 7 A. Well, so a POSA would have been aware of hierarchical  
11:04:38 8 approaches that favored stronger, more commonly used acids.

11:04:42 9 Q. What does the term "hierarchical approach" refer to?

11:04:45 10 A. A stepwise approach.

11:04:48 11 Q. Was that approach described in the literature?

11:04:50 12 A. Yes, it was.

11:04:53 13 Q. Would you turn in your binder to Tab 4 where you'll  
11:04:56 14 find DTX-167?

11:04:59 15 A. I'm there.

11:05:00 16 Q. Would you please identify this document?

11:05:01 17 A. This is the Bighley reference.

11:05:10 18 Q. Turning to Page 480 of Bighley -- or Bighley, we'll  
11:05:14 19 go with Bighley -- can you read when we get there -- let me  
11:05:18 20 know when you're at Page 480.

11:05:20 21 A. 480?

11:05:21 22 Q. 4 -8 -0.

11:05:23 23 And I'll direct your attention to the last two  
11:05:26 24 sentences of the first paragraph.

11:05:33 25 A. Okay, I'm there.

Koleng - Direct

11:05:36 1 Q. Would you please read the last two sentences of the  
11:05:38 2 first paragraph on Page 480 of Bighley?

11:05:41 3 A. "Hence, there is a need for a decision tree to create  
11:05:45 4 a prototype thought process whereby a suitable salt form can  
11:05:49 5 be chosen in an efficient and timely manner with few false  
11:05:54 6 starts and the minimum expenditure of resources. The  
11:05:58 7 following decision tree (Figure 1) is proposed to aid in  
11:06:01 8 this selection."

11:06:03 9 Q. Now, if we turn to the next page, 481 in Bighley,  
11:06:09 10 what's shown here?

11:06:09 11 A. This is the decision tree that was referenced in the  
11:06:14 12 passage we just read.

11:06:16 13 Q. How, if at all, does this decision tree and this  
11:06:18 14 excerpt from Bighley compare with your personal experience  
11:06:22 15 with salt screening?

11:06:23 16 A. It's consistent.

11:06:24 17 Q. Based on the approach shown in Bighley, would a -- or  
11:06:28 18 which acid would a skilled artisan have begun with?

11:06:30 19 A. Hydrogen chloride.

11:06:32 20 Q. And what are the reasons that a skilled artisan would  
11:06:34 21 have begun with hydrogen chloride?

11:06:36 22 A. As we've heard during testimony, it's a very strong  
11:06:39 23 acid. It's very common in pharmaceutical salts. And the  
11:06:44 24 counterion, the chloride, is not one that would be expected  
11:06:47 25 to react readily with other parts of the compound.

Koleng - Direct

11:06:52 1 Q. Based on the approach shown in Bighley, where would a  
11:06:56 2 skilled artisan have turned after hydrogen chloride?

11:06:59 3 A. As we look down, to other mineral acid salts.

11:07:04 4 Q. And what are mineral acid salts?

11:07:08 5 A. There's salts of mineral acids where mineral acids  
11:07:10 6 are also -- often called inorganic acids.

11:07:13 7 Q. What are inorganic acids?

11:07:15 8 A. Those that typically don't include carbon.

11:07:22 9 Q. Can you please provide an example or two of some  
11:07:25 10 inorganic acids or mineral acids?

11:07:28 11 A. Sure. Other examples include hydrogen bromide, for  
11:07:32 12 instance. Sulfuric acid, nitric acid, phosphoric acid,  
11:07:36 13 among others.

11:07:37 14 Q. What are the reasons a skilled artisan would have  
11:07:39 15 considered inorganic acids or mineral acids at this stage in  
11:07:42 16 the decision tree?

11:07:43 17 A. First, they're still very strong acids. The other  
11:07:47 18 reason would be that they didn't find -- they weren't either  
11:07:51 19 able to form a salt with the hydrogen chloride. Or any  
11:07:54 20 resulting salt didn't display any beneficial properties.

11:07:59 21 Q. Now, I'd like to you to turn in Bighley to Page 486.  
11:08:03 22 It's a little bit further into the reference. And I'll  
11:08:09 23 direct your attention to the paragraph under preparation of  
11:08:13 24 organic salts.

11:08:15 25 Do you see that section?

Koleng - Direct

11:08:15 1 A. I do.

11:08:16 2 Q. Do you recall Dr. Steed's testimony that a skilled  
11:08:18 3 artisan would have disfavored inorganic acids based on this  
11:08:22 4 excerpt from the Bighley reference?

11:08:23 5 A. I do.

11:08:24 6 Q. What's your response to that testimony?

11:08:25 7 A. I believe that it's misplaced. If we consider the  
11:08:29 8 context of this entire paragraph, the POSA would recognize  
11:08:34 9 that it's specifically addressing an issue associated with  
11:08:37 10 salt selection for injectable drugs, those that are  
11:08:41 11 typically administered as solutions and injected directly  
11:08:45 12 into the body.

11:08:46 13 Q. Are -- this is straightforward, but are oral dosage  
11:08:50 14 forms injectable drugs?

11:08:51 15 A. No.

11:08:51 16 Q. Is Cabometyx an injectable drug?

11:08:54 17 A. No.

11:08:58 18 Q. Now, if we turn back to the decision tree, which I  
11:09:01 19 believe is on Page 481. As part of the hierarchical  
11:09:09 20 approach, described in Bighley, would a skilled artisan have  
11:09:13 21 considered organic acids?

11:09:14 22 A. Potentially.

11:09:15 23 Q. Under what circumstances would a skilled artisan have  
11:09:18 24 considered organic acids?

11:09:19 25 A. Well, we have, one, if you're developing an



Koleng - Direct

11:09:21 1 injectable product. Number two, you weren't able to obtain  
11:09:27 2 either salts with the inorganic acids. Or there's any salt  
11:09:32 3 that was obtained didn't have desirable properties.

11:09:36 4 Q. Can you please provide an example or two of an  
11:09:40 5 organic acid?

11:09:40 6 A. Sure. These would be things like maleic acid,  
11:09:45 7 methane sulfonic acid, for instance.

11:09:48 8 Q. Now, what type of organic acids would have been  
11:09:50 9 considered at this stage in the decision tree?

11:09:52 10 A. Stronger ones, like the examples I gave.

11:09:54 11 Q. And why is that?

11:09:55 12 A. Again, because you're still looking for stronger  
11:09:58 13 acids.

11:10:01 14 Q. Would you turn to PDX 5.13, please?

11:10:06 15 What's displayed on the demonstrative?

11:10:08 16 A. So organic acids have limitations in their use as  
11:10:13 17 counterions. This is a list of four that a POSA would need  
11:10:16 18 to consider.

11:10:17 19 Q. Could you describe some of the limitations?

11:10:19 20 A. Sure. They're usually weaker. They have higher  $pK_a$ s  
11:10:24 21 than the inorganic acids. They themselves have reduced  
11:10:29 22 aqueous solubility. They typically include multiple  
11:10:32 23 functional groups that can complicate the chemistry or have  
11:10:35 24 side reactions, things of that nature. And they usually  
11:10:37 25 have larger molecular weights, which add bulk to the API

Koleng - Direct

11:10:42 1 which can create issues in formulating products.

11:10:45 2 Q. Have organic acids been used in pharmaceutical salts?

11:10:48 3 A. Yes, they have.

11:10:49 4 Q. Turning to PDX-5.14. What were the most common  
11:10:54 5 organic acids used?

11:10:56 6 A. As shown here, mesylate, maleate, the citrate,  
11:11:00 7 tartrate, and acetate.

11:11:02 8 Q. What type of acid is malic acid?

11:11:05 9 A. Organic.

11:11:06 10 Q. Is malic acid included in the list of the five most  
11:11:11 11 common organic acids on PDX-5.14?

11:11:14 12 A. No.

11:11:16 13 Q. Did you hear Dr. Steed's testimony that malic acid  
11:11:18 14 would have been favored over other potential acids because  
11:11:21 15 it was identified as generally recognized as safe?

11:11:24 16 A. I recall that testimony.

11:11:26 17 Q. Have you ever considered a GRAS designation in  
11:11:30 18 identifying a counterion for selection in a salt screen?

11:11:32 19 A. No.

11:11:33 20 Q. What are the reasons for that?

11:11:34 21 A. Mainly that the GRAS designation, GRAS regulations  
11:11:38 22 are related to food additives of the pure materials. It's  
11:11:42 23 really not directly applicable to pharmaceuticals. The  
11:11:46 24 other consideration is that the combination of a counterion  
11:11:50 25 and the active ingredient are qualified together. So that

Koleng - Direct

11:11:54 1 it's the safety and toxicity of the salt, not the starting  
11:11:58 2 counterion acid in this case.

11:12:00 3 It's a particularly -- particularly interesting  
11:12:02 4 to note that the two most common anions listed here,  
11:12:07 5 actually their corresponding acids are non-GRAS designated.

11:12:10 6 Q. Now, turning to PDX-5.15.

11:12:13 7 Do you agree with Dr. Steed that malate salts  
11:12:16 8 were commonly used in pharmaceutical compounds?

11:12:18 9 A. No, I do not agree with him.

11:12:20 10 Q. What are the reasons you disagree?

11:12:22 11 A. Mainly that the information that -- part of what's  
11:12:25 12 already been put up during this trial shows that it was only  
11:12:27 13 rarely used.

11:12:28 14 Q. Now, I want to direct your attention to -- back to  
11:12:33 15 Tab 4 in your materials, which is DTX-167, the Bighley  
11:12:37 16 reference we discussed earlier.

11:12:39 17 A. Yes, sir.

11:12:39 18 Q. Can you turn to Page 453?

11:12:48 19 A. I'm there.

11:12:49 20 Q. And turning your attention to the second-to-last  
11:12:52 21 paragraph on the page, what information is addressed in  
11:12:56 22 Table 1 in Bighley?

11:12:57 23 A. "Salt forms that have been clinically evaluated in  
11:13:00 24 humans or were commercially marketed through 1993."

11:13:06 25 Q. Now, turn the page to Pages 454 and 455.

Koleng - Direct

11:13:12 1 Do you find Table 1?

11:13:13 2 A. I do.

11:13:15 3 Q. What is the name of Table 1?

11:13:16 4 A. Anionic pharmaceutical salt forms currently in use.

11:13:21 5 Q. And what is an anionic pharmaceutical salt form?

11:13:25 6 A. So this is a salt where the active ingredient is a  
11:13:29 7 base and the corresponding counterion comes from an acid,  
11:13:33 8 like cabozantinib (L)-malate.

11:13:36 9 Q. Have you analyzed the salts in Table 1?

11:13:38 10 A. I have.

11:13:40 11 Q. Can you turn to Tab 5 in your materials, where you'll  
11:13:43 12 find PTX-782?

11:13:48 13 Can you please identify this document?

11:13:50 14 A. Yeah, so this is the data from Table 1 that we just  
11:13:55 15 reviewed. Table 1 presented it alphabetically. This table  
11:14:00 16 that shows the -- the same salt, the same anionic salts but  
11:14:07 17 ranked by frequency of occurrence.

11:14:09 18 Q. So, I think you may have just said two different  
11:14:12 19 things.

11:14:12 20 How are the salts arranged in this table on  
11:14:15 21 PTX-782?

11:14:17 22 A. By order of occurrence. So, from most current to  
11:14:21 23 least current, least -- most frequent to least frequent.

11:14:24 24 Q. Now, focusing on the anionic salts in PTX-782, how  
11:14:30 25 many salts are listed here?

Koleng - Direct

11:14:31 1 A. I believe 113.

11:14:36 2 MR. YURKERWICH: Mr. Lee, can you write the  
11:14:37 3 number 113 on the -- PTX-782?

11:14:37 4 BY MR. YURKERWICH:

11:14:45 5 Q. Are these 113 salts all pharmaceutically acceptable  
11:14:49 6 salts?

11:14:49 7 A. Yes.

11:14:52 8 Q. Now, I want to direct your attention to the bottom  
11:14:54 9 left of the table. And focus your attention on the malate  
11:14:54 10 salt.

11:15:02 11 How often was the malate salt used in  
11:15:04 12 pharmaceutical -- anionic pharmaceutical salts?

11:15:07 13 A. As highlighted here, it's 0.26 percent.

11:15:10 14 Q. Now, coming back and taking a look at the whole  
11:15:13 15 chart, how many anions used in 1 percent or fewer  
11:15:18 16 pharmaceutical salts?

11:15:19 17 A. I believe it's about 98.

11:15:29 18 Q. Would you turn in your materials to Tab 6. We're  
11:15:34 19 going to take a quick look at another reference that's been  
11:15:36 20 discussed. You'll find DTX-177.

11:15:40 21 Would you please identify that document?

11:15:41 22 A. This is the Paulekuhn reference that's been in  
11:15:46 23 evidence.

11:15:46 24 Q. Now, if you look on -- farther down on the first page  
11:15:50 25 of this reference, do you see the section "Study Design"?

Koleng - Direct

11:15:52 1 A. I do.

11:15:57 2 Q. What kind of compounds were studied in the Paulekuhn  
11:16:00 3 reference?

11:16:00 4 A. So as they note here, they studied chemically  
11:16:03 5 well-defined APIs. They would be drug substances. They  
11:16:06 6 represent about 1,300 from the FDA Orange Book at the time.

11:16:11 7 Q. Now, turning two pages forward to Page 6667, do you  
11:16:16 8 find Table 2.

11:16:17 9 A. I do.

11:16:19 10 Q. What is the title of Table 2?

11:16:20 11 A. "Distribution of Anions Used in APIs of Category I."

11:16:27 12 Q. Can you remind us, what is Category I?

11:16:30 13 A. Yes. These would be the same sorts of anionic  
11:16:33 14 pharmaceutical salts we just discussed. The API is basic.  
11:16:36 15 The counterion comes from an acid.

11:16:39 16 Q. Now, focusing on the first column in Table 2 and  
11:16:43 17 looking at the malate entry, how often was the malate salt  
11:16:48 18 used in terms of the overall sample studied?

11:16:51 19 A. 0.4 percent. I believe you have the -- there we go.

11:16:56 20 Q. And if you look to the right-hand side of the  
11:16:59 21 column -- or the right -- far right column in Table 2, how  
11:17:04 22 often was the malate salt used between 2002 and 2006?

11:17:08 23 A. Once. It was roughly 3 percent of 36 drugs approved  
11:17:13 24 during that period.

11:17:14 25 Q. Did you reach any conclusions based on your review of

Koleng - Direct

11:17:16 1 the Bighley and Paulekuhn references?

11:17:19 2 A. Yes, that the malate salt is only rarely used.

11:17:22 3 Q. How does that compare with your experience?

11:17:24 4 A. It compares correctly. It's not one I've ever  
11:17:28 5 considered.

11:17:29 6 Q. How many of your salt screen projects included malic  
11:17:32 7 acids among the acids tested?

11:17:34 8 A. None.

11:17:36 9 Q. By 2009, how many acids were known and could have  
11:17:39 10 been considered by a skilled artisan in attempting to form a  
11:17:42 11 pharmaceutically acceptable salt?

11:17:44 12 A. Bighley lists at least 113.

11:17:49 13 Q. Can you please turn to Tab 7 in your binder where  
11:17:52 14 you'll find DTX-287? Would you please identify this  
11:17:57 15 document?

11:17:58 16 A. This is the Sutent product label.

11:18:03 17 Q. What is Sutent?

11:18:05 18 A. It's a pharmaceutical composition comprising  
11:18:08 19 sunitinib malate.

11:18:10 20 Q. Do you recall Dr. Steed's testimony that a skilled  
11:18:12 21 artisan would have been motivated to use malic acid because  
11:18:15 22 the active ingredient in Sutent is in the form of malate  
11:18:20 23 salt?

11:18:20 24 A. I recall that.

11:18:22 25 Q. What's your response to that?

Koleng - Direct

11:18:24 1 A. I disagree. Although Sutent has a similar  
11:18:29 2 indication, a POSA doesn't select counterions based on  
11:18:34 3 indication. It's based upon the actual attributes of the  
11:18:39 4 chemical that they're studying.

11:18:40 5 Q. Well, let's talk about some of those attributes. I  
11:18:43 6 want to direct your attention to the second paragraph on the  
11:18:44 7 first page of DTX-287. Would you please read the first  
11:18:48 8 sentence in that paragraph?

11:18:49 9 A. "Sunitinib malate is a yellow to orange powder with a  
11:18:54 10  $pK_a$  of 8.95."

11:18:57 11 Q. How do the chemical properties of sunitinib compare  
11:19:01 12 to cabozantinib?

11:19:02 13 A. With this  $pK_a$ , sunitinib would be would have been  
11:19:08 14 considered a strong base even relative to cabozantinib.

11:19:11 15 Q. And what are the consequences of that difference.

11:19:15 16 A. Well, first, the choice of acids that one would  
11:19:18 17 consider would be different. And then the like -- the  
11:19:23 18 likely outcomes would be different.

11:19:28 19 Q. Turning to PDX-5.16, what is your third opinion  
11:19:32 20 you're offering here today?

11:19:33 21 A. Pharmaceutical development is a complex process.  
11:19:38 22 There has to be a range of considerations that go into  
11:19:42 23 identifying the pharmaceutical salt, if selected, that  
11:19:46 24 ultimately goes into the final products.

11:19:48 25 Q. Can you give us some examples of considerations or



Koleng - Direct

11:19:52 1 factors in development that would have been considered in  
11:19:55 2 the course of salt development in 2009?

11:19:58 3 A. Yes. I believe we've heard several already. They  
11:20:02 4 include elements such as bioavailability, solubility,  
11:20:06 5 dissolution, physical and chemical stability, the PK  
11:20:11 6 potentially resulting from that particular salt.  
11:20:14 7 Manufacturability is key as well, among others.

11:20:17 8 Q. Now, let's assume the skilled artisan wanted to make  
11:20:19 9 a salt with a favorable solubility. Could a skilled artisan  
11:20:23 10 have had a reasonable expectation as to what salt would give  
11:20:26 11 the best solubility?

11:20:28 12 A. No.

11:20:30 13 Q. In your experience, does making a salt result in  
11:20:33 14 improved solubility relative to the free form of the active  
11:20:37 15 ingredient?

11:20:37 16 A. No. Not always.

11:20:40 17 Q. Dr. Steed testified that a skilled artisan would have  
11:20:42 18 been motivated to pursue a malate salt of cabozantinib to  
11:20:45 19 improve solubility. What impact did forming a malate salt  
11:20:48 20 actually have on solubility of cabozantinib?

11:20:51 21 A. As we've learned, the solubility in biorelevant media  
11:20:57 22 which is more predictive of bioavailability, was not  
11:21:00 23 greater.

11:21:00 24 Q. How, if at all, does that bear on your opinion  
11:21:03 25 regarding reasonable expectation of success?

Koleng - Direct

11:21:05 1 A. Again, I don't believe it supports a POSA having a  
11:21:09 2 reasonable expectation of success.

11:21:10 3 Q. What is your overall response to Dr. Steed's  
11:21:13 4 testimony that it would have been obvious to prepare the  
11:21:17 5 (L)-malate salt of cabozantinib as part of a salt screen?

11:21:19 6 A. First, I don't think, from everything we just  
11:21:22 7 discussed, they wouldn't have been motivated to evaluate it.  
11:21:26 8 And they wouldn't have had a reasonable expectation of  
11:21:29 9 success.

11:21:30 10 MR. YURKERWICH: Thank you, Dr. Koleng. I have  
11:21:32 11 no further questions for you at this time.

11:21:33 12 Your Honor, Exelixis would move to admit  
11:21:36 13 PTX-373, PTX-782, and DTX-287.

11:21:43 14 MR. MATHAS: No objection, Your Honor.

11:21:44 15 THE COURT: Admitted without objection.

11:21:46 16 (PTX Exhibit No. 373 and 782 were admitted into  
11:21:46 17 evidence.)

11:21:46 18 (DTX Exhibit No. 287 was admitted into  
11:21:52 19 evidence.)

11:21:52 20 MR. MATHAS: Your Honor, may we hand up a cross  
11:21:54 21 binder?

11:21:55 22 THE COURT: Sure.

11:22:05 23 THE WITNESS: Are you going to reference  
11:22:06 24 anything in here? Otherwise, I'll put it on the floor.

11:22:09 25 MR. MATHAS: I may. So go ahead and keep it

Koleng - Cross

11:22:11 1 handy. This other one is small.

11:22:17 2 THE WITNESS: Thank you, sir.

11:22:13 3 CROSS-EXAMINATION

11:22:20 4 BY MR. MATHAS:

11:22:21 5 Q. All right. Good morning, Dr. Koleng.

11:22:23 6 A. Good morning, sir.

11:22:24 7 Q. Now, as of 2009, the basic principles associated with  
11:22:29 8 salt formation reactions were understood; isn't that true?

11:22:32 9 A. I believe acid base reactions were reasonably  
11:22:37 10 understood.

11:22:38 11 Q. All right. And by 2009, salt screening was a known  
11:22:44 12 technique for identifying salt forms of compounds; true?

11:22:47 13 A. It's a -- it's a way to identify salt forms, yes.

11:22:53 14 Q. All right. And it was a known technique as of 2009;  
11:22:56 15 right?

11:22:56 16 A. Yes.

11:22:59 17 Q. And you yourself, as of 2009, were involved in doing  
11:23:03 18 salt screening; right?

11:23:03 19 A. Correct.

11:23:05 20 Q. And as of 2009, a salt screen would have been a tool  
11:23:08 21 in the formulator's toolbox; isn't that true?

11:23:11 22 A. Yes.

11:23:12 23 Q. All right. Now, I want to -- you gave some opinions  
11:23:17 24 about variables -- excuse me -- variables that would be  
11:23:21 25 considered in setting up a salt screen.

Koleng - Cross

11:23:24 1 Do you recall that?

11:23:25 2 A. I do.

11:23:25 3 Q. And you testified, I believe, that salt screening is  
11:23:32 4 unpredictable because you couldn't predict or guarantee the  
11:23:35 5 results of the salt screen; is that your testimony?

11:23:38 6 A. It's unpredictable. Yes.

11:23:41 7 Q. Okay. And because you say it's unpredictable, you  
11:23:44 8 say you can't guarantee that a salt will form; right?

11:23:47 9 A. Correct.

11:23:48 10 Q. And you say you can't guarantee what the properties  
11:23:51 11 of the salt will be in advance; right?

11:23:53 12 A. Correct.

11:23:55 13 Q. Okay. Now, a person of ordinary skill in the art  
11:23:58 14 would have been able to assess these variables that you  
11:24:01 15 talked about and select suitable conditions to conduct a  
11:24:05 16 salt screen, wouldn't they?

11:24:06 17 A. I believe they would have the capability to, you  
11:24:12 18 know, set up the experiment, react to the data, make the  
11:24:16 19 necessary changes on a trial and error basis, yes.

11:24:19 20 Q. And they would have been able to do that as of 2009,  
11:24:21 21 wouldn't they?

11:24:22 22 A. Yes.

11:24:24 23 Q. You also talked about a hierarchical order of  
11:24:30 24 proceeding through a salt screen.

11:24:31 25 Do you recall that?

Koleng - Cross

11:24:32 1 A. I do.

11:24:33 2 Q. And you pulled up the Bighley reference, and there  
11:24:35 3 was a decision tree in there that you talked about; right?

11:24:38 4 A. Correct.

11:24:40 5 Q. Now, but you agree, don't you, Dr. Koleng that a  
11:24:43 6 person of ordinary skill in the art as of 2009 would not  
11:24:46 7 have been beholden to following prior art decision trees in  
11:24:51 8 a hierarchical order in setting up a salt screen?

11:24:55 9 A. Correct.

11:24:56 10 Q. All right. You also talked about the fact that malic  
11:25:01 11 acid was a weak acid; right?

11:25:02 12 A. Correct.

11:25:03 13 Q. Okay. Now, you agree that there are a significant  
11:25:06 14 number of organic acids that have been used to make  
11:25:10 15 pharmaceutically acceptable salts, don't you?

11:25:12 16 A. Bighley shows a fair number, yes.

11:25:16 17 Q. All right. And you highlighted a couple of those in  
11:25:18 18 your testimony; right?

11:25:19 19 A. Correct.

11:25:20 20 Q. Okay. And you also talked a little bit about the  
11:25:32 21 Tong's Rule-of-2 and the use of  $pK_a$  during your direct;  
11:25:36 22 right?

11:25:36 23 A. I don't think I specifically addressed Tong's  
11:25:39 24 Rule-of-2. I said I acknowledge that I heard Dr. Steed's  
11:25:43 25 testimony and I was aware of the principle.

Koleng - Cross

11:25:46 1 Q. Okay. So you're aware of the principle of using  $pK_a$   
11:25:49 2 for selecting salts for a salt screen; right?

11:25:51 3 A. As one variable, yes.

11:25:53 4 Q. And that was something you were aware of back in  
11:25:55 5 2009; right?

11:25:56 6 A. Correct.

11:25:57 7 Q. And something that the POSA would have been aware of  
11:25:59 8 back in 2009?

11:26:00 9 A. I believe so, yes.

11:26:01 10 Q. Okay. Now, it's true, isn't it, Dr. Koleng, that a  
11:26:05 11 POSA could have determined the  $pK_a$  of a compound by  
11:26:09 12 performing a titration test; right?

11:26:11 13 A. Potentially, yes.

11:26:13 14 Q. And that's a routine test that POSAs like yourself as  
11:26:17 15 of 2009 would have been able to perform and interpret;  
11:26:20 16 right?

11:26:20 17 A. It was a test in use at that time, yes.

11:26:23 18 Q. Okay. Now, you showed us an entry on quinolines in  
11:26:27 19 connection with their  $pK_a$ ; is that right?

11:26:30 20 A. Correct.

11:26:31 21 Q. And you didn't show us an entry on the  $pK_a$  of  
11:26:35 22 cabozantinib; isn't that right?

11:26:37 23 A. That's correct. It wasn't available at the 2009  
11:26:40 24 time.

11:26:40 25 Q. Right. And so when you said that the quinolines

Koleng - Cross

11:26:43 1 wouldn't have fallen within the  $pK_a$  of a Rule-of-2, that was  
11:26:49 2 quinolines generally. You weren't saying that cabozantinib  
11:26:52 3 wouldn't fall within the Rule-of-2; right?

11:26:53 4 A. That's correct. It's what would have been available  
11:26:56 5 without experimentation.

11:26:58 6 Q. Right. And you're not disputing, are you, sir, that  
11:27:01 7 cabozantinib falls within the Rule-of-2?

11:27:03 8 A. Ultimately, correct.

11:27:05 9 Q. Okay. And I think you said this, but just so the  
11:27:17 10 record is very clear, you agree, Dr. Koleng, that malate  
11:27:22 11 salt is a pharmaceutically acceptable salt; right?

11:27:25 12 A. Yes.

11:27:26 13 Q. And you agree that as of 2009, malate salt had been  
11:27:30 14 used in FDA-approved drugs; right?

11:27:32 15 A. A small number, yes.

11:27:35 16 Q. They had been used in FDA-approved drugs since at  
11:27:37 17 least the 1970s; true?

11:27:39 18 A. I believe there's one going that far back, yes.

11:27:41 19 Q. Okay. And malate salt had been used in FDA-approved  
11:27:44 20 drugs in the decade leading up to the priority date here;  
11:27:47 21 right?

11:27:47 22 A. In the small numbers that I showed, yes.

11:27:50 23 Q. Okay. Now, there was some discussion about malic  
11:27:53 24 acid and whether it was GRAS or not.

11:27:56 25 Do you recall that?

Koleng - Cross

11:27:56 1 A. I do.

11:27:57 2 Q. And that's G-R-A-S, generally recognized as safe;  
11:28:01 3 right?

11:28:01 4 A. Right.

11:28:02 5 Q. And I think what you said on your direct was, "Well,  
11:28:06 6 GRAS isn't relevant because that's just something that  
11:28:08 7 matters for food additives"; is that right?

11:28:10 8 A. No. I said that GRAS status is specific for foods  
11:28:14 9 and it's not a consideration that I've ever taken into  
11:28:18 10 account.

11:28:18 11 Q. Okay. Now, but persons of ordinary skill as of 2009  
11:28:22 12 did take into account the GRAS status of counterions in  
11:28:26 13 selecting salts for salt screening. Didn't they?

11:28:28 14 A. I don't think I'd agree with that generally.

11:28:31 15 Q. Okay. Now -- well, let me ask you this: As of 2009,  
11:28:35 16 isn't it true that the literature taught the GRAS status of  
11:28:38 17 counterions and to consider it in selecting salts for  
11:28:42 18 development?

11:28:43 19 A. So they have GRAS designation like in some of the  
11:28:47 20 experiment -- like in some of the literature that's been put  
11:28:49 21 up? It was -- it wasn't -- not every salt was GRAS. I  
11:28:54 22 think it's one of consideration, if it was important to a  
11:28:56 23 POSA. But it's obviously not -- it doesn't -- it's not a  
11:29:01 24 definitive no if it's not GRAS designated.

11:29:04 25 Q. All right. So let's look at -- let's look at some of



Koleng - Cross

11:29:07 1 that literature then.

11:29:07 2 MR. MATHAS: Can we pull up PTX-610, please?

11:29:07 3 BY MR. MATHAS:

11:29:10 4 Q. And we'll put it on the screen here, Dr. Koleng.

11:29:16 5 This is the Stahl reference that's been

11:29:16 6 discussed --

11:29:18 7 MR. YURKERWICH: Your Honor.

11:29:21 8 THE COURT: Yes.

11:29:21 9 MR. YURKERWICH: We object. The document now

11:29:23 10 before the witness isn't in the cross binder.

11:29:25 11 MR. MATHAS: We can hand up a copy, Your Honor,

11:29:27 12 if we may.

11:29:28 13 THE COURT: Okay.

11:29:29 14 MR. MATHAS: It's in a bunch of these other

11:29:30 15 binders. I didn't know we were going to talk about it, but

11:29:33 16 here we are.

11:29:34 17 BY MR. MATHAS:

11:29:35 18 Q. All right. So this is the Stahl reference,

11:29:38 19 Dr. Koleng?

11:29:39 20 A. Is that a question or a statement?

11:29:40 21 Q. Either. That's what it is; right?

11:29:43 22 A. Yes.

11:29:45 23 Q. And you were in the courtroom for Dr. Steed's

11:29:48 24 testimony about this?

11:29:48 25 A. Yes.

Koleng - Cross

11:29:49 1 Q. And you referenced in an answer a moment ago that  
11:29:51 2 there might be some tables that had GRAS status indicated;  
11:29:55 3 right?

11:29:55 4 A. Yes.

11:29:55 5 Q. Okay. Now, this -- this reference is -- it's in the  
11:29:59 6 *Handbook of Pharmaceutical Salts*; right?

11:30:01 7 A. I'm sure we're going to get to that.

11:30:05 8 Q. All right. It's not the *Handbook of Food Additives*;  
11:30:09 9 right?

11:30:09 10 A. Agreed.

11:30:10 11 Q. Okay. And let's go back to one of the tables that  
11:30:13 12 Dr. Steed showed that maybe you were -- you were referring  
11:30:17 13 to a moment ago.

11:30:18 14 MR. MATHAS: And I think we can find that back  
11:30:20 15 in Table 2, which begins on Page 336 of the exhibit.

11:30:33 16 THE WITNESS: So 336?

11:30:34 17 BY MR. MATHAS:

11:30:34 18 Q. Well, it's -- it's the Bates page 33 -- or the  
11:30:37 19 Exhibit Page 336, Document Page 334.

11:30:40 20 A. I'm looking for the document page. Yeah.

11:30:46 21 Q. The page number on the bottom middle of the page has  
11:30:49 22 the 336.

11:30:50 23 A. All right.

11:30:56 24 Q. Did you find Table 1 there?

11:30:57 25 A. Well -- oh, you're -- it's 334 on the document.

Koleng - Cross

11:31:05 1 Yes, I'm there.

11:31:06 2 Q. Okay. So Table 1 starts there on -- on Exhibit  
11:31:12 3 Page 336. And then if you go forward, Table 2 starts on  
11:31:17 4 Exhibit Page 338.

11:31:19 5 Are you with me?

11:31:20 6 A. Table 2 on 336 you said. Okay. Yeah.

11:31:25 7 Q. All right. And Table 2 is a list of acids sorted by  
11:31:29 8 increasing  $pK_a$  value. That's been looked at; right?

11:31:33 9 A. The table says "Acids sorted by increasing  $pK_a$   
11:31:38 10 value."

11:31:38 11 Q. Okay. And in this list of acids in this textbook on  
11:31:43 12 pharmaceutical salts, in the far right-hand there's a column  
11:31:47 13 on GRAS status; right?

11:31:48 14 A. I see that.

11:31:50 15 Q. All right. And that's information that would have  
11:31:51 16 been available to the person of ordinary skill in the art as  
11:31:55 17 of 2009; right?

11:31:57 18 A. This reference would suggest so.

11:31:59 19 Q. Okay. And persons of ordinary skill in the art could  
11:32:03 20 have used this information about whether or not a compound  
11:32:06 21 was GRAS or not in determining counterions to include in a  
11:32:13 22 salt screen; right?

11:32:14 23 A. If they were concerned about the GRAS status, yes.

11:32:17 24 MR. MATHAS: Okay. And if we can go to Page 334  
11:32:20 25 of the exhibit.

Koleng - Cross

11:32:20 1 BY MR. MATHAS:

11:32:27 2 Q. You see there there's a section GRAS and ADI?

11:32:32 3 A. Okay.

11:32:32 4 Q. All right. And so --

11:32:34 5 A. Sorry. What page?

11:32:37 6 Q. Your -- it's?

11:32:37 7 A. Now we're in text. I thought you said the table.

11:32:39 8 I'm sorry. Oh, here we go. Okay.

11:32:41 9 Q. Yeah. There's a section here, GRAS and ADI.

11:32:45 10 Are you with me?

11:32:46 11 A. I do.

11:32:47 12 Q. Okay. And this is a section on GRAS in this -- in  
11:32:51 13 this text on the *Handbook of Pharmaceutical Salts*; right?

11:32:54 14 A. Okay.

11:32:56 15 Q. And so this -- this textbook that would have been  
11:32:59 16 known to the POA about selecting pharmaceutical salts  
11:33:02 17 includes a section on GRAS; right, Dr. Koleng?

11:33:05 18 A. Yes.

11:33:07 19 Q. Actually -- oh, sorry.

11:33:07 20 A. As shown here.

11:33:08 21 Q. And look at second sentence there.

11:33:11 22 MR. MATHAS: Let's call that out.

11:33:11 23 BY MR. MATHAS:

11:33:12 24 Q. This textbook says that, "Some substances may be  
11:33:15 25 considered unobjectionable because they are used profusely

Koleng - Cross

11:33:18 1 in food processing"; right?

11:33:21 2 A. Okay.

11:33:22 3 Q. That's what it says. You agree?

11:33:23 4 A. I see the words. I agree with the words.

11:33:25 5 Q. And you --

11:33:26 6 A. I agree the words are there.

11:33:28 7 Q. Right. And this is talking about substances being

11:33:32 8 unobjectable for use as pharmaceutical salts because of

11:33:34 9 their GRAS status; isn't that right?

11:33:37 10 A. No. I'm going to say that it's -- some substance

11:33:41 11 here refer to the acid not the pharmaceutical salt.

11:33:44 12 Q. Okay.

11:33:45 13 A. Which includes the combination of the API and the

11:33:48 14 base and the salt.

11:33:49 15 Q. Okay. So, the -- the acids may be considered

11:33:54 16 unobjectionable in the salt screen because of their GRAS

11:33:57 17 status. That's what it's teaching?

11:33:59 18 A. Well, they would be unobjectable on themselves, how

11:34:04 19 they're used in a salt screen, et cetera, within it.

11:34:07 20 Ultimately, the resulting drug substance would still have to

11:34:09 21 be assessed.

11:34:10 22 Q. All right. Now, in -- and you're not disputing that

11:34:12 23 malic acid was known and recognized as GRAS as of the

11:34:16 24 priority date here; right?

11:34:17 25 A. No, I'm not.

Koleng - Cross

11:34:19 1 MR. MATHAS: No further questions.

11:34:20 2 THE COURT: Dr. Koleng --

11:34:24 3 THE WITNESS: Yes, sir.

11:34:25 4 THE COURT: -- if you had a base and you didn't  
11:34:28 5 know what its  $pK_a$  was, how much effort goes into determining  
11:34:34 6 that?

11:34:34 7 THE WITNESS: It can be quite a bit. So, you  
11:34:38 8 can start with what's known about the functionality and then  
11:34:42 9 you can then work from there. So, that gives you an idea of  
11:34:46 10 the -- functionality gives you an idea where to start and  
11:34:48 11 then I don't disagree that you could run experimentation to  
11:34:52 12 identify the  $pK_a$  ultimately. Yeah, the ionization constant  
11:34:58 13 for that base.

11:34:59 14 The issue would be is that it depends on the  
11:35:01 15 conditions under which it's conducted and the -- and the  
11:35:03 16 test to do it. So, you would still have to do enough  
11:35:06 17 experimentation to gets an accurate value, so there's -- you  
11:35:09 18 may be able to improve the estimate, but work would continue  
11:35:13 19 to try to fine tune that.

11:35:15 20 THE COURT: So if you wanted to do that and you  
11:35:17 21 had a fully equipped lab and you were a person of ordinary  
11:35:21 22 skill, how many days, weeks, months, years would you set  
11:35:25 23 aside to do that?

11:35:26 24 THE WITNESS: I would say a couple weeks.

11:35:31 25 THE COURT: All right. The solvent streams

Koleng - Cross

11:35:38 1 where if you had, again, your base and you wanted to find  
11:35:44 2 out what solvent would work with it, how long does it take  
11:35:47 3 to do the solvent screening?

11:35:50 4 THE WITNESS: The solvent screenings can take on  
11:35:52 5 the order of a couple weeks as well because you have to  
11:35:55 6 select the solvent, you have to prep the samples, have  
11:35:57 7 analytical methodology in order to assess the amount that is  
11:36:00 8 dissolved, prepare the samples, analyze the samples, and  
11:36:03 9 then get the results.

11:36:05 10 THE COURT: All right.

11:36:07 11 MR. YURKERWICH: No redirect, Your Honor.

11:36:09 12 THE COURT: Okay. All right. Dr. Koleng, thank  
11:36:12 13 you. You're done. Please watch your step.

11:36:14 14 THE WITNESS: Thank you, sir.

11:36:19 15 MR. PRUSSIA: Your Honor, Plaintiffs call  
11:36:21 16 Dr. Bernhardt Trout.

11:36:24 17 THE COURT: All right.

11:36:32 18 DEPUTY CLERK: Please state and spell your full  
11:36:46 19 name for the record.

11:36:46 20 THE WITNESS: Bernhardt Trout.

11:36:51 21 B-E-R-N-H-A-R-D-T, T-R-O-U-T.

11:36:51 22 BERNHARDT TROUT, the witness herein, after  
11:36:51 23 having been duly sworn under oath, was examined and  
11:37:04 24 testified as follows:

11:37:04 25 THE WITNESS: Yes, I do.

Trout - Direct

11:37:19 1 MR. PRUSSIA: May I proceed?

11:37:12 2 DIRECT EXAMINATION

11:37:12 3 BY MR. PRUSSIA:

11:37:21 4 Q. Good morning. Would you please introduce yourself to  
11:37:24 5 the Court?

11:37:24 6 A. Good morning. My name is Bernhardt Trout.

11:37:28 7 Q. Dr. Trout, have you been retained by Exelixis as an  
11:37:31 8 expert witness in this case?

11:37:32 9 A. Yes, I have.

11:37:33 10 Q. Are you being compensated for your work in this case?

11:37:35 11 A. Yes, I am.

11:37:37 12 Q. Does your compensation depend on the outcome or the  
11:37:40 13 substance of your opinions?

11:37:41 14 A. No.

11:37:41 15 MR. PRUSSIA: Let's please have PDX-2.

11:37:44 16 BY MR. PRUSSIA:

11:37:44 17 Q. Where do you work, sir?

11:37:45 18 A. I work at MIT. It's Massachusetts Institute of  
11:37:48 19 Technology.

11:37:50 20 Q. And what is your position at MIT?

11:37:51 21 A. I'm a professor of chemical engineering.

11:37:54 22 Q. And how long have you been a professor of chemical  
11:37:56 23 engineering?

11:37:57 24 A. Over 25 years.

11:37:59 25 Q. What is your educational background?



Trout - Direct

11:38:00 1 A. Well, I got my undergraduate degree and my master's  
11:38:03 2 degree at MIT. My Ph.D. at the University of California,  
11:38:07 3 Berkeley in 1996. All in chemical engineering.

11:38:11 4 And then I did a post-doctoral research at the  
11:38:13 5 Max-Planck Institute in Stuttgart, Germany.

11:38:17 6 Q. Generally, what are your job responsibilities as a  
11:38:20 7 professor of chemical engineering at MIT?

11:38:23 8 A. Well, generally there are three aspects. One is  
11:38:24 9 research, run a research lab. Another is education, meaning  
11:38:30 10 specifically classroom room teaching, which I also do. And  
11:38:33 11 then the third area is service, helping the department, and  
11:38:37 12 the institute in committees and other ways.

11:38:39 13 Q. You mentioned teaching. What is the primary focus of  
11:38:42 14 your teaching?

11:38:42 15 A. Well, chemical engineering.

11:38:44 16 Q. And are there any courses that you've taught that are  
11:38:46 17 relevant to the issues in this case?

11:38:47 18 A. Yeah. Yes, there are. I've taught, for example,  
11:38:50 19 thermodynamics at the undergraduate and graduate level.  
11:38:54 20 I've taught chemical kinetics and reactor design, again, at  
11:38:57 21 the undergraduate and graduate level. I've taught process  
11:39:01 22 laboratory and a whole host of other courses.

11:39:03 23 Q. You mentioned research. What is the focus of your  
11:39:06 24 research?

11:39:06 25 A. Well, the focus is pharmaceutical development and

Trout - Direct

11:39:10 1 manufacturing research.

11:39:11 2 Q. What experience do you have with crystalline  
11:39:14 3 pharmaceutical salts?

11:39:15 4 A. Well, I have quite a bit of experience in my own lab  
11:39:18 5 at MIT and also as a consultant with pharmaceutical  
11:39:22 6 companies.

11:39:23 7 Q. What type of consulting work do you do?

11:39:25 8 A. Well, there are two aspects. One is kind of  
11:39:29 9 higher-level consulting as, for example, serving on a  
11:39:32 10 scientific advisory board. And then the other aspect is  
11:39:36 11 helping companies solve kind of targeted technical problems.

11:39:39 12 Q. And generally what type of companies do you work  
11:39:42 13 with?

11:39:42 14 A. Generally larger companies, companies we'd be  
11:39:47 15 familiar with. But also medium size and smaller and  
11:39:50 16 startups.

11:39:50 17 Q. If you could please take a look at your binder at  
11:39:54 18 Tab 1, it's PTX-774.

11:39:56 19 Would you please identify it?

11:39:56 20 A. Yes. That is my CV.

11:40:02 21 Q. And does it contain an accurate summary of your  
11:40:04 22 education and professional experience?

11:40:06 23 A. Yes.

11:40:07 24 MR. PRUSSIA: With that, Your Honor, I tender  
11:40:08 25 Dr. Trout as an expert in pharmaceutical development and

Trout - Direct

11:40:11 1 manufacturing, including with respect to crystallization of  
11:40:14 2 pharmaceutical salts.

11:40:17 3 MR. LOMBARDI: No objection.

11:40:18 4 THE COURT: All right. You may proceed.

11:40:18 5 BY MR. PRUSSIA:

11:40:19 6 Q. Let's move into your opinions, sir.

11:40:20 7 MR. PRUSSIA: Let's please have PDX-3.

11:40:20 8 BY MR. PRUSSIA:

11:40:22 9 Q. What issues will you be addressing today?

11:40:24 10 A. Well, I'm going to be responding to MSN's experts  
11:40:28 11 and, in particular, Dr. Steed with respect to written  
11:40:32 12 description, and also obviousness-type double patenting.

11:40:34 13 MR. PRUSSIA: Can I have the next slide, please,  
11:40:36 14 PDX-4?

11:40:36 15 BY MR. PRUSSIA:

11:40:37 16 Q. What does this slide show?

11:40:38 17 A. Well, this shows the cover page of the three asserted  
11:40:42 18 crystalline malate salt patents. The '439, the '440, and  
11:40:47 19 the '015, together with the cover page of the respective  
11:40:52 20 file histories.

11:40:52 21 Q. And have you reviewed the file histories for these  
11:40:55 22 patents?

11:40:55 23 A. Yes, I have.

11:40:57 24 Q. And if you look in your binder at Tabs 2, 3, and 4,  
11:41:00 25 they are JTX-1, 2, and 3.

Trout - Direct

11:41:01 1 Could you just briefly identify what those are?

11:41:04 2 A. Yes. 2, 3, and 4 are respectively those three  
11:41:09 3 patents in the same order.

11:41:11 4 Q. And what do these patents generally disclose?

11:41:13 5 A. Well, they generally disclose crystalline  
11:41:16 6 cabozantinib malate.

11:41:18 7 Q. What is the priority date for these patents?

11:41:20 8 A. Priority date is January 16th, 2009.

11:41:28 9 Q. And have you offered an opinion regarding the  
11:41:30 10 qualifications of a person of ordinary skill in the art for  
11:41:32 11 these patents as of that date?

11:41:34 12 A. Yes, I have.

11:41:35 13 MR. PRUSSIA: And if we turn to PDX-5.

11:41:35 14 BY MR. PRUSSIA:

11:41:38 15 Q. What qualifications would that person have?

11:41:39 16 A. Well, that person would have had at least a  
11:41:42 17 bachelor's degree in chemistry, chemical engineering,  
11:41:46 18 pharmaceutical sciences, or a related discipline. Along  
11:41:49 19 with several years of experience working in pharmaceutical  
11:41:52 20 development and/or solid-state chemistry.

11:41:55 21 And a POSA would have also been part of a team  
11:41:58 22 which would have included synthetic organic chemists and  
11:42:01 23 process chemists, formulation scientists, and analytical  
11:42:05 24 scientists, and clinicians.

11:42:07 25 Q. And did you apply this definition of a person of

Trout - Direct

11:42:11 1 skill in connection with forming your opinions in this case?

11:42:13 2 A. Yes, I did.

11:42:13 3 Q. And you understand that MSN has in -- and its expert  
11:42:16 4 has offered a different opinion?

11:42:17 5 A. Yes, I do.

11:42:18 6 Q. And would your opinions change regardless of which  
11:42:20 7 definition is adopted?

11:42:21 8 A. No, they wouldn't.

11:42:22 9 Q. And as of the priority date, did you meet the  
11:42:25 10 qualifications of a person of ordinary skill in the art  
11:42:26 11 under either side's definition?

11:42:28 12 A. Yes.

11:42:29 13 Q. Now, let's move into -- before moving into your  
11:42:31 14 opinions, let's briefly cover some background concepts,  
11:42:34 15 okay?

11:42:34 16 A. Okay.

11:42:35 17 MR. PRUSSIA: Let's move to PDX-6.

11:42:35 18 BY MR. PRUSSIA:

11:42:38 19 Q. What is shown on this slide?

11:42:39 20 A. This is a very high-level slide, Your Honor. But it,  
11:42:43 21 I think, presents the starting point for understanding these  
11:42:46 22 patents. I think we're all familiar, but the starting point  
11:42:49 23 here is that there are three important states of matter.  
11:42:52 24 Solid, liquid, and gas.

11:42:55 25 Q. And what's the relevant state for this case?

Trout - Direct

11:42:57 1 A. It's a solid.

11:42:58 2 MR. PRUSSIA: And if we could turn to PDX-7.

11:42:58 3 BY MR. PRUSSIA:

11:43:01 4 Q. What are the different types of solids?

11:43:02 5 A. Well, there are two different types of solids. I  
11:43:05 6 think Your Honor's heard that throughout the first part of  
11:43:08 7 the week here.

11:43:09 8 On the left, I have the crystalline solid. You  
11:43:12 9 can see in the large circle, it's a cartoon emblematic of  
11:43:18 10 the repeating pattern of the atoms and molecules over three  
11:43:22 11 dimensions in crystalline material. And that smaller insert  
11:43:27 12 is an actual picture of an actual crystal, you can see the  
11:43:31 13 facets there.

11:43:33 14 On the other hand, there's amorphous material,  
11:43:36 15 and you can see that on the right side. So the amorphous  
11:43:39 16 material does not contain long-range order. There's a  
11:43:43 17 randomness there. And then you can see there's a picture,  
11:43:46 18 again, from -- a microscope picture of an amorphous  
11:43:51 19 material. It looks very different.

11:43:52 20 MR. PRUSSIA: So let's turn to PDX-8.

11:43:52 21 BY MR. PRUSSIA:

11:43:54 22 Q. What is shown here?

11:43:55 23 A. These are the asserted claims of the crystalline  
11:43:58 24 malate salt patents.

11:43:59 25 Q. And what are the common elements of the three

Trout - Direct

11:44:01 1 asserted claims?

11:44:02 2 A. Well, first of all -- well, you can see highlighted  
11:44:05 3 here, crystalline, also the chemical formula cabozantinib,  
11:44:09 4 and then the malate.

11:44:12 5 MR. PRUSSIA: Can we turn to JTX-1. It's Tab 2  
11:44:15 6 in the binder. It's the '439 patent. And if we turn to  
11:44:18 7 Scheme 1. Which begins at Column 19.

11:44:18 8 BY MR. PRUSSIA:

11:44:23 9 Q. What is Compound I?

11:44:25 10 A. Compound I is cabozantinib (L)-malate.

11:44:33 11 MR. PRUSSIA: And if we turn to Column 5 of the  
11:44:35 12 patent, there's a structure starting at Line 50.

11:44:35 13 BY MR. PRUSSIA:

11:44:40 14 Q. What is that structure?

11:44:40 15 A. That structure is (L)-malic acid.

11:44:45 16 MR. PRUSSIA: And if we turn to the next column,  
11:44:47 17 there's a structure starting at Line 1.

11:44:47 18 BY MR. PRUSSIA:

11:44:50 19 Q. What is that structure?

11:44:51 20 A. That structure is (D)-malic acid.

11:44:55 21 Q. And what is the difference between the (L)- and the  
11:44:58 22 (D)-malic acid?

11:44:58 23 A. Well, the two are mirror images of each other.

11:45:02 24 MR. PRUSSIA: Let's go back to Column 6 and look  
11:45:06 25 at a paragraph that starts at about Line 56.

Trout - Direct

11:45:06 1 BY MR. PRUSSIA:

11:45:11 2 Q. Do you see the phrase "this disclosure relates to  
11:45:14 3 malic salts"?

11:45:14 4 A. Yes.

11:45:16 5 Q. What malic salts are disclosed in this paragraph of  
11:45:19 6 the patents?

11:45:20 7 A. Well, there are three starting at Line 59; the  
11:45:25 8 (L)-malate salt of cabozantinib, the (D)-malate salt of  
11:45:29 9 cabozantinib, and the (DL)-malate salt of cabozantinib.

11:45:33 10 Q. So, what, if any, significance would a skilled person  
11:45:36 11 have attributed to the patent's use of the term "malate  
11:45:39 12 salts" here?

11:45:40 13 A. Well, as the patent shows right here, the malate  
11:45:43 14 salts are those three salts.

11:45:46 15 MR. PRUSSIA: If we turn to Column 7.

11:45:46 16 BY MR. PRUSSIA:

11:45:49 17 Q. What does the first sentence in the paragraph  
11:45:52 18 beginning at Line 10 say about the malate salts addressed in  
11:45:56 19 these patents?

11:45:56 20 A. That line says, "The salts of cabozantinib, and  
11:46:02 21 particularly Compound I" -- again, that's the cabozantinib  
11:46:06 22 (L)-malate -- "have a preferred combination of  
11:46:09 23 pharmaceutical properties for development."

11:46:12 24 Q. And if we turn to the second sentence, what  
11:46:15 25 properties are described there?



Trout - Direct

11:46:16 1 A. Well, under two different conditions of temperature  
11:46:20 2 and relative humidity, Compound I, again, cabozantinib  
11:46:24 3 (L)-malate, showed no change in assay, purity, moisture, and  
11:46:29 4 dissolution.

11:46:31 5 Q. And continuing to the next sentence, at Line 16, what  
11:46:34 6 properties are described there?

11:46:35 7 A. "The DSC/TGA" -- so those are thermal analytical  
11:46:41 8 methods -- "showed the Compound (I) to be stable up to  
11:46:44 9 185 degrees Celsius.

11:46:46 10 Q. So what, if any, significance would a skilled person  
11:46:49 11 have attributed to these disclosures in the crystalline  
11:46:52 12 malate salt patent?

11:46:53 13 A. Well, the crystalline cabozantinib (L)-malate is  
11:46:59 14 stable and, in general, it has good pharmaceutical  
11:47:03 15 properties for development.

11:47:05 16 Q. Now, if we turn to the sentence beginning at Line 21  
11:47:09 17 of this same paragraph, and it starts with "the (L)-malate  
11:47:13 18 salt," what properties are described there?

11:47:16 19 A. Well, it says the (L)-malate salt was synthesized  
11:47:21 20 with good yield and purity and had sufficient solubility for  
11:47:24 21 use in a pharmaceutical composition.

11:47:27 22 Q. And what, if any, significance would a person of  
11:47:30 23 skill have attributed to that disclosure in the patent?

11:47:33 24 A. Well, again, that is suitable for a  
11:47:34 25 manufacturability, it could be manufactured. And it had

Trout - Direct

11:47:37 1 suitable properties for use in a pharmaceutical composition,  
11:47:41 2 in particular, solubility.

11:47:43 3 Q. Look at the last sentence of this paragraph, at  
11:47:46 4 Column 7, Lines 26 to 31. What does this sentence convey to  
11:47:51 5 a skilled person regarding the (D)- and (L)-malate salts?

11:47:55 6 A. Well, this sentence says, "The (D)-malate salt of  
11:47:59 7 cabozantinib will have the same properties as the (L)-malate  
11:48:03 8 salt of cabozantinib."

11:48:05 9 MR. PRUSSIA: If we move over to Column 8 at  
11:48:09 10 Lines 34 to 39.

11:48:09 11 BY MR. PRUSSIA:

11:48:11 12 Q. What does this passage disclose about the properties  
11:48:13 13 of the crystalline cabozantinib (D)-malate?

11:48:17 14 A. Yeah. Okay. It says, "As known in the art, the  
11:48:24 15 crystalline (D)-malate salt will form the same crystalline  
11:48:27 16 form and have the same properties as crystalline compound  
11:48:32 17 (1)" -- in other words, the (L)-malate salt.

11:48:34 18 MR. PRUSSIA: Let's take a look at Table 1 in  
11:48:37 19 this patent. Table 1 spans two columns. I want to focus on  
11:48:41 20 the right-hand side, which is on Column 8.

11:48:41 21 BY MR. PRUSSIA:

11:48:43 22 Q. Do you see the reference to (L)-malate salt in the  
11:48:46 23 bottom row?

11:48:47 24 A. Yes, I do.

11:48:48 25 Q. What information does Table 1 disclose concerning the

Trout - Direct

11:48:51 1 (L)-malate salt of cabozantinib?

11:48:52 2 A. Well, it discloses the solubility. And then it says  
11:48:55 3 that it's crystalline, nonhygroscopic with no indication of  
11:49:00 4 hydrate formation. It's got suitable solubility. And  
11:49:03 5 chemical and physical stability.

11:49:05 6 Q. How do the properties of the (L)-malate salt compare  
11:49:08 7 to the properties of the other salts disclosed in Table 1?

11:49:10 8 A. Well, as the patent teaches, the properties  
11:49:13 9 altogether show that it has the most suitable suite or  
11:49:16 10 combination of properties for pharmaceutical development.

11:49:20 11 Q. Was cabozantinib malate the most soluble salt?

11:49:22 12 A. No.

11:49:23 13 Q. And were you here in Court yesterday for the  
11:49:25 14 testimony of Dr. Khalid Shah?

11:49:27 15 A. Yes, I was.

11:49:28 16 Q. What was the explanation he provided for why Exelixis  
11:49:31 17 pursued the (L)-malate salt despite its low solubility?

11:49:35 18 A. Well, even though it doesn't have the best solubility  
11:49:37 19 and, in general, has a low solubility, it has the best  
11:49:41 20 combination of properties.

11:49:43 21 Q. Staying on Column 8, there's a paragraph right below  
11:49:45 22 this table. Please read the first sentence there beginning  
11:49:49 23 at Line 25.

11:49:50 24 A. Certainly. "Another aspect of this disclosure  
11:49:53 25 relates to crystalline forms of Compound (I), which include

Trout - Direct

11:49:57 1 the N-1 and/or the N-2 crystalline form of Compound (I), as  
11:50:02 2 described herein."

11:50:04 3 Q. So, a couple things on this sentence. First, there's  
11:50:06 4 a reference to crystalline form, we're seeing that for the  
11:50:09 5 first time. What is a crystalline form?

11:50:11 6 A. Well, a crystalline form is a particular polymorph or  
11:50:15 7 a particular repeating pattern of a given crystal.

11:50:19 8 Q. Now, this sentence starts with the phrase "another  
11:50:23 9 aspect." What, if any, significance would a skilled person  
11:50:26 10 attach to the use of the term "another aspect of this  
11:50:28 11 disclosure"?

11:50:29 12 A. Well, the skilled person would understand that the  
11:50:31 13 inventors are saying in addition and separate to crystalline  
11:50:37 14 cabozantinib (L)-malate salt, another aspect of the  
11:50:41 15 disclosure relates to the specific crystalline polymorphic  
11:50:46 16 forms, the N-1 and the N-2.

11:50:49 17 Q. Can you please read the next sentence?

11:50:51 18 A. Certainly. "Each form of Compound (I) is a separate  
11:50:55 19 aspect of the disclosure."

11:50:58 20 Q. What, if any, significance would a skilled person  
11:51:01 21 attach to the patents' use of the term "separate aspect of  
11:51:04 22 the disclosure"?

11:51:05 23 A. Well, I think this is -- just reinforces the previous  
11:51:08 24 sentence that, again, it's a separate aspect of the  
11:51:11 25 disclosure or separate aspect of the invention. The

Trout - Direct

11:51:15 1 specific crystalline polymorphic forms, the N-1 and N-2,  
11:51:20 2 separate from crystalline cabozantinib (L)-malate.

11:51:24 3 Q. Now, do any of the crystalline malate salt patents  
11:51:27 4 contain claims to an N-1, N-2, or any other crystalline  
11:51:31 5 forms?

11:51:31 6 A. No.

11:51:34 7 Q. Let's talk more about the word "crystalline." What  
11:51:36 8 is the plain and ordinary meaning of the term "crystalline"  
11:51:39 9 in the context of the asserted claims?

11:51:41 10 A. Well, it's what I just said when we had the slide up  
11:51:45 11 for crystalline. It's a solid material in which there's a  
11:51:50 12 regular repeating pattern over -- many over three dimensions  
11:51:54 13 and over large spatial dimensions in contrast to an  
11:51:58 14 amorphous form. And it's consistent with what I heard  
11:52:01 15 Dr. Steed say yesterday.

11:52:02 16 Q. Dr. Steed used slightly different words. He said --  
11:52:05 17 I wrote it down -- "a crystal in which the structural units  
11:52:08 18 are repeated regularly in three dimensions."

11:52:11 19 Do you remember that testimony?

11:52:11 20 A. Yes, I do.

11:52:13 21 Q. Is there a meaningful difference between that and  
11:52:15 22 your plain and ordinary meaning?

11:52:16 23 A. No.

11:52:18 24 Q. How many crystalline cabozantinib salts exist?

11:52:22 25 A. Well, there are three. There's the (L)-malate, the

Trout - Direct

11:52:26 1 (D)-malate and the (DL)-malate.

11:52:28 2 Q. And what is the basis for that opinion?

11:52:30 3 A. Well, that's what's written and disclosed in the  
11:52:34 4 patent.

11:52:35 5 MR. PRUSSIA: And if you pull back up Column 6,  
11:52:38 6 Line 56.

11:52:38 7 BY MR. PRUSSIA:

11:52:38 8 Q. Is this the passage that you're referring to?

11:52:42 9 MR. PRUSSIA: We can highlight "this disclosure  
11:52:44 10 related to" -- yeah.

11:52:45 11 THE WITNESS: Yes, it is. Again, that's the  
11:52:47 12 disclosure of malate salts.

11:52:47 13 BY MR. PRUSSIA:

11:52:50 14 Q. Now, Dr. Steed testified yesterday that the claims  
11:52:54 15 require a genus of crystalline malate salt forms.

11:52:58 16 Do you remember that?

11:52:59 17 A. Yes. I do.

11:53:00 18 Q. Do the claims require a genus of crystalline malate  
11:53:03 19 salt forms?

11:53:04 20 A. No.

11:53:06 21 Q. And why not?

11:53:07 22 A. Well, the word "form," first of all, is not in the  
11:53:10 23 claims. And the claims do not require a particular genus of  
11:53:14 24 specific polymorphs. They just require the property of  
11:53:18 25 crystalline and, of course, cabozantinib malate.

Trout - Direct

11:53:21 1 MR. PRUSSIA: Let's look back at the claims,  
11:53:23 2 PDX-8.

11:53:23 3 BY MR. PRUSSIA:

11:53:24 4 Q. And just to be clear, you just testified to this, but  
11:53:26 5 I have to ask the question: Do any of the asserted claims  
11:53:29 6 contain the word "form"?

11:53:30 7 A. No.

11:53:32 8 MR. PRUSSIA: Let's turn to PDX-9.

11:53:32 9 BY MR. PRUSSIA:

11:53:35 10 Q. What is shown here?

11:53:35 11 A. Well, this is Claim 1 on the right and left of two  
11:53:42 12 different patents, not the asserted crystalline malate  
11:53:46 13 cabozantinib patents. This on the left is the '776 patent,  
11:53:52 14 and on the right is the '549 patent. These are in the same  
11:53:56 15 family as the asserted crystalline cabozantinib and malate  
11:54:00 16 patents, and they have the same specification.

11:54:03 17 Q. Do the claims in these patents contain the word  
11:54:06 18 "form"?

11:54:06 19 A. Yes.

11:54:08 20 Q. How, if at all, does that bear on your opinions in  
11:54:10 21 this case?

11:54:10 22 A. Well, again, this is from the same inventors and the  
11:54:14 23 same family, so it shows, I guess, as additional evidence of  
11:54:19 24 what I was talking about before, that the inventors could  
11:54:22 25 have claimed forms if they wanted to, and, in fact, they

Trout - Direct

11:54:26 1 did.

11:54:27 2 MR. PRUSSIA: So returning to PDX-8, and we're  
11:54:30 3 looking at the claims of the crystalline malate salt  
11:54:33 4 patents.

11:54:33 5 BY MR. PRUSSIA:

11:54:34 6 Q. How was the term "crystalline" being used in the  
11:54:37 7 asserted claims?

11:54:38 8 A. Well, crystalline meaning that they're a solid.  
11:54:42 9 They're crystalline as I've been defining it, and they're  
11:54:46 10 not amorphous.

11:54:47 11 Q. Now, as of the priority date, would a skilled person  
11:54:49 12 have been able to distinguish between a crystalline material  
11:54:52 13 and an amorphous material?

11:54:54 14 A. Yes.

11:54:56 15 MR. PRUSSIA: Let's have PDX-10, please.

11:54:56 16 BY MR. PRUSSIA:

11:54:59 17 Q. Just explain for the Court, please, how a skilled  
11:55:01 18 person would have done that.

11:55:02 19 A. Well, this is an example of via microscopy. That's  
11:55:07 20 one method. And the Court can, I think, see and  
11:55:12 21 distinguish, but between the amorphous and crystalline, just  
11:55:15 22 by looking at it. The crystalline has these facets. That's  
11:55:19 23 a consequence of the regular repeating pattern where the  
11:55:22 24 amorphous does not.

11:55:24 25 Q. Yesterday we heard some discussion about different



Trout - Direct

11:55:26 1 forms. Now, as of the priority date, could a person of  
11:55:30 2 skill in the art identify a crystalline salt without knowing  
11:55:33 3 what specific form the salt was in?

11:55:36 4 A. Yes.

11:55:37 5 Q. And how does this relate to your opinions regarding  
11:55:40 6 written description?

11:55:40 7 A. Well, again, because crystalline is exactly as I've  
11:55:45 8 been explaining it -- and this is an example of a method  
11:55:48 9 that the skilled person could use to distinguish between  
11:55:51 10 crystalline and amorphous without knowing, you could see it  
11:55:54 11 quite plainly there without knowing what specific  
11:55:58 12 crystalline or amorphous material it is.

11:56:01 13 Q. Now, what would a skilled person have done if the --  
11:56:04 14 that person wanted to evaluate the particular polymorph,  
11:56:08 15 polymorphic form?

11:56:09 16 A. Well, the person could use other techniques, for  
11:56:13 17 example, more detailed analysis with X-ray powder  
11:56:17 18 diffraction. I think the Court might be familiar with this.  
11:56:19 19 It was discussed earlier this week.

11:56:22 20 Q. Now -- so let's turn now to your opinions regarding  
11:56:25 21 written description, and what is your opinion regarding  
11:56:27 22 whether the specification conveys that the inventors  
11:56:30 23 possessed the claimed invention?

11:56:31 24 A. Well, my opinion is, for the reasons that I've been  
11:56:35 25 given, that the inventors did possess the claimed invention.

Trout - Direct

11:56:39 1 Q. Is there any dispute that the specification discloses  
11:56:42 2 cabozantinib?

11:56:43 3 A. No.

11:56:44 4 Q. Is there any dispute that the specification discloses  
11:56:47 5 cabozantinib malate salts?

11:56:48 6 A. No.

11:56:50 7 MR. PRUSSIA: Let's turn to the crystalline  
11:56:51 8 limitation, and let's have PDX-11.

11:56:51 9 BY MR. PRUSSIA:

11:56:54 10 Q. Does the specification disclose crystalline salts?

11:56:57 11 A. Yes. And I have here in this table a summary of the  
11:57:02 12 various places in the patent specification in which it's  
11:57:06 13 disclosed. You can see there are quite a few. I won't list  
11:57:10 14 all of them verbally.

11:57:11 15 Q. You have a reference to preparative examples on the  
11:57:15 16 right-hand side of this table. What is disclosed by the  
11:57:20 17 preparative examples?

11:57:21 18 A. Well, by preparative examples, I mean, the examples  
11:57:25 19 in the patent that are named and listed as examples in which  
11:57:29 20 they describe actual chemical processes to generate  
11:57:34 21 crystalline cabozantinib (L)-malate. And for that matter  
11:57:38 22 one of the examples generates the amorphous version of the  
11:57:41 23 material.

11:57:42 24 MR. PRUSSIA: If we could put up DDX Steed 13.

11:57:42 25 BY MR. PRUSSIA:

Trout - Direct

11:57:45 1 Q. Now, yesterday Dr. Steed offered the opinion that no  
11:57:48 2 two forms are representative of one another because of the  
11:57:52 3 different intrinsic properties of crystalline salt forms.

11:57:55 4 Do you recall that?

11:57:55 5 A. Yes, I do.

11:57:56 6 Q. Now, two questions about this. First, is that  
11:57:59 7 opinion relevant under the plain and ordinary meaning of  
11:58:02 8 crystalline?

11:58:02 9 A. No.

11:58:04 10 Q. Second, is that opinion correct?

11:58:06 11 A. No.

11:58:07 12 Q. And can you explain why?

11:58:08 13 A. Yes. Certainly. So, as I said, under the -- plain  
11:58:13 14 and ordinary meaning of crystalline, it's not relevant at  
11:58:15 15 all. But if we assume for some reason that form is read  
11:58:19 16 into the claim, then the patents disclosed representative  
11:58:24 17 species of those crystalline forms.

11:58:27 18 Q. So, let's turn to that.

11:58:29 19 Would your opinion concerning written  
11:58:30 20 description change if Dr. Steed's version of the claims were  
11:58:33 21 applied?

11:58:33 22 A. No.

11:58:35 23 Q. Let's have PDX-12, please. And at a high level, what  
11:58:38 24 are the reasons that your opinion is unchanged under his  
11:58:41 25 view?

Trout - Direct

11:58:41 1 A. Well, as I just said, representative crystalline  
11:58:44 2 forms are disclosed in the specification. In addition to  
11:58:48 3 that, the purported forms that the Court heard about  
11:58:52 4 yesterday are not distinct forms.

11:58:55 5 And, finally, there are common structural  
11:58:57 6 features disclosed in the specification.

11:58:59 7 Q. So if you go to PDX-13 and start with your first  
11:59:03 8 reason, what are the representative forms of cabozantinib  
11:59:06 9 salts?

11:59:07 10 A. Well, those are the N-1, N-2 forms explicitly  
11:59:11 11 disclosed in the specification which are the  
11:59:14 12 pharmaceutically most relevant forms.

11:59:15 13 Q. And what makes forms N-1 and N-2 representative  
11:59:19 14 polymorphs?

11:59:20 15 A. Well, they exhibit properties that make them suitable  
11:59:23 16 for pharmaceutical development.

11:59:25 17 Q. What are those properties?

11:59:26 18 A. Well, the properties are what we discussed before.  
11:59:29 19 They're crystalline, so they have good crystallinity.  
11:59:33 20 Nonhygroscopic, they have good stability, both chemical and  
11:59:37 21 physical.

11:59:38 22 Q. Generally, you mentioned stability. Generally what  
11:59:40 23 role does stability play in identifying a pharmaceutically  
11:59:43 24 relevant form?

11:59:44 25 A. Well, stability is very important. The API, as we've

Trout - Direct

11:59:49 1 heard throughout the week, in its pharmaceutical  
11:59:52 2 composition, needs to be stable over the lifetime of the  
11:59:55 3 drug. Otherwise, it wouldn't be a good drug. It wouldn't  
11:59:58 4 be useable.

11:59:59 5 Q. Now, we walked through the specification of the  
12:00:02 6 crystalline malate salt patents. There are also figures.  
12:00:04 7 We didn't show the Court those, but have you considered the  
12:00:07 8 figures?

12:00:07 9 A. Yes, I have.

12:00:08 10 Q. What do the figures disclose regarding the stability  
12:00:10 11 of forms N-1 and N-2?

12:00:12 12 A. Well, the figures disclose that they have good  
12:00:15 13 thermal stability. So they're stable thermally.

12:00:19 14 MR. PRUSSIA: Let's turn to PDX-14.

12:00:19 15 BY MR. PRUSSIA:

12:00:22 16 Q. And your second reason, what is your response  
12:00:24 17 regarding the other purported forms that he identified?

12:00:26 18 A. Well, I went through those forms in detail that  
12:00:31 19 Dr. Steed identified yesterday. They're all disclosed in my  
12:00:35 20 report. My conclusion is that those purported forms are not  
12:00:40 21 distinct forms, at least there's no clear evidence that  
12:00:42 22 they're distinct forms.

12:00:44 23 MR. PRUSSIA: Can we have the next slide,  
12:00:46 24 PDX-15?

12:00:46 25 BY MR. PRUSSIA:

Trout - Direct

12:00:47 1 Q. Now, there's a reference to XRPD overlay. Could you  
12:00:51 2 start please by explaining to the Court what that is?

12:00:53 3 A. Yes. And I think Your Honor is familiar with XRPDs.  
12:00:59 4 I'm sure you've heard of them before and earlier this week.  
12:01:02 5 So these are diffractograms or the products of an X-ray  
12:01:07 6 powdered fraction experiment, and actually it might be  
12:01:11 7 helpful.

12:01:11 8 THE WITNESS: May I use my laser pointer?

12:01:13 9 THE COURT: Sure, yes.

12:01:14 10 THE WITNESS: Okay. So, again, I know it's  
12:01:17 11 basic, but there are various peaks. I'll focus on the  
12:01:20 12 bottom one, and this combination of peaks across the X-axis  
12:01:25 13 gives an indication of a specific crystalline or polymorphic  
12:01:30 14 form. And the overlay is if I take two of these and put  
12:01:35 15 them together, make sure the x-axis is the same scale, and  
12:01:39 16 so, that's what I've done here on this slide.

12:01:42 17 Q. Now, who prepared this overlay?

12:01:44 18 A. I did.

12:01:44 19 Q. And based on what data?

12:01:46 20 A. Well, the blue curve is based on MSN's data for their  
12:01:51 21 purported form M. And the orange curve is based on  
12:01:55 22 Exelixis' data for its free base Form 3. In other words,  
12:02:00 23 not cabozantinib (L)-malate.

12:02:02 24 Q. So, what conclusions did you reach about whether form  
12:02:07 25 M is a true crystalline salt form of cabozantinib malate?

Trout - Direct

12:02:11 1 A. Well, that it's not. You can see from the overlay  
12:02:14 2 the peaks match. In other words, MSN's purported form M is  
12:02:19 3 a free base form, the free base Form III, not a salt, not a  
12:02:26 4 malate salt.

12:02:26 5 Q. Now, did Dr. Steed point to form M as a purported  
12:02:30 6 form?

12:02:30 7 A. He did originally.

12:02:32 8 Q. And what's your understanding of his reliance on form  
12:02:35 9 M now?

12:02:36 10 MR. LOMBARDI: So, Your Honor, I'm just going to  
12:02:37 11 object because now Dr. Steed didn't present this at trial.  
12:02:41 12 So, it's irrelevant, I guess.

12:02:45 13 There shouldn't be any mistake. Dr. Steed did  
12:02:48 14 not present anything about form M at trial, didn't say it  
12:02:51 15 was crystalline form.

12:02:52 16 THE COURT: I forget what I'm -- is that like  
12:02:55 17 form S or something?

12:02:57 18 MR. LOMBARDI: Yes, form S.

12:02:59 19 So this is something that was never presented.

12:03:01 20 THE COURT: Right. I think the relevant  
12:03:03 21 universe is the 111 that he did present.

12:03:06 22 MR. PRUSSIA: Your Honor, the next question will  
12:03:09 23 get to the point of this; right?

12:03:09 24 BY MR. PRUSSIA:

12:03:10 25 Q. So he initially relied on it, but now he doesn't

Trout - Direct

12:03:13 1 because of why?

12:03:16 2 Why doesn't -- why doesn't Dr. -- why -- what's  
12:03:18 3 your understanding as to why Dr. Steed did not present this  
12:03:20 4 form to the Court, even though he initially presented it in  
12:03:23 5 his opinions?

12:03:23 6 MR. LOMBARDI: Your Honor, that would have been  
12:03:25 7 a question for Dr. Steed.

12:03:26 8 THE COURT: Well, I tend to think it is but it's  
12:03:27 9 hard to say without hearing what the answer is. So, I  
12:03:30 10 reserve the right to strike the answer after I hear it.

12:03:33 11 So, I'm sorry. You may want the question  
12:03:37 12 re-asked.

12:03:38 13 THE WITNESS: Maybe one more time, counsel,  
12:03:39 14 please.

12:03:39 15 BY MR. PRUSSIA:

12:03:40 16 Q. What is your understanding as to why Dr. Steed no  
12:03:42 17 longer relies on this form?

12:03:44 18 A. I think he agrees with me that it's not a true form.  
12:03:47 19 It's actually not a form of cabozantinib (L)-malate salt.

12:03:51 20 MR. PRUSSIA: Let's have PTX-16.

12:03:53 21 THE WITNESS: Polymorphic forms.

12:03:54 22 THE COURT: So I'm not going to strike it, it's  
12:03:56 23 just irrelevant. So we'll just continue.

12:03:59 24 MR. PRUSSIA: PDX-16, please.

12:03:59 25 BY MR. PRUSSIA:



Trout - Direct

12:04:01 1 Q. What does this slide show?

12:04:02 2 A. Okay. So this is XRPD pattern for purported Mylan  
12:04:07 3 form M-1. Dr. Steed did have this explicitly in his table,  
12:04:12 4 although he didn't show the Court this particular  
12:04:16 5 diffractogram.

12:04:16 6 Q. And what conclusions did you reach whether form M-1  
12:04:19 7 is a true form?

12:04:20 8 A. Well, I think you can see in contrast to the previous  
12:04:26 9 XRPD diffractograms, this has this broad halo indicative of  
12:04:32 10 amorphous material. It does have some broad features here  
12:04:36 11 which show that there's some kind of crystalline material.  
12:04:40 12 It's not fully amorphous, it seems primarily amorphous, but  
12:04:44 13 it's unclear what this material is. Certainly not clear  
12:04:47 14 that it's a new form.

12:04:50 15 Q. Now --

12:04:51 16 A. It's not a new crystalline polymorphic form. I  
12:04:55 17 should be careful myself.

12:04:56 18 That's not a new crystalline polymorphic form.

12:04:56 19 Q. So, generally, what is your opinion regarding form  
12:04:58 20 M-1 and the other forms that Dr. Steed identified?

12:05:00 21 A. Well, I went through them in some detail. Again, I  
12:05:05 22 outlined it in multiple pages of my report.

12:05:08 23 In going through each of those forms from Mylan  
12:05:10 24 and Cipla, my conclusion is there's no clear evidence that  
12:05:14 25 these are new or distinct forms. The evidence says that

Trout - Direct

12:05:18 1 they're not.

12:05:19 2 Q. Now, do you recall Dr. Steed's testimony concerning  
12:05:22 3 solvates?

12:05:22 4 A. Yes.

12:05:23 5 Q. And what is your response to that?

12:05:25 6 A. Well, there's no evidence that there's actual  
12:05:30 7 solvates of crystalline cabozantinib (L)-malate.

12:05:33 8 MR. PRUSSIA: Let's have PDX-17.

12:05:33 9 BY MR. PRUSSIA:

12:05:36 10 Q. Move to your third point.

12:05:37 11 What is that?

12:05:38 12 A. That there are common structural features disclosed  
12:05:40 13 in the specification.

12:05:42 14 MR. PRUSSIA: And let's have PDX-18.

12:05:42 15 BY MR. PRUSSIA:

12:05:44 16 Q. What are those common structural features?

12:05:46 17 A. Well, there's the structure, meaning that they're  
12:05:52 18 crystalline, as opposed to amorphous. There's the formula,  
12:05:55 19 like what you can see up on the screen. The cabozantinib  
12:05:59 20 malate. And then there's the actual name, the chemical name  
12:06:03 21 also in the specification.

12:06:05 22 Q. Now, to just be clear, what's -- when you reference  
12:06:08 23 structure, what are you referring to?

12:06:09 24 A. Oh, that it's crystalline.

12:06:11 25 Q. Now, do these structural features allow a skilled

Trout - Direct

12:06:14 1 artisan to recognize and identify other crystalline  
12:06:18 2 cabozantinib salts?

12:06:19 3 A. Yes.

12:06:19 4 Q. Which, if any, of these structural features are  
12:06:21 5 present in form N-1?

12:06:23 6 A. All of them.

12:06:24 7 Q. Which are present in form N-2?

12:06:26 8 A. All of them.

12:06:27 9 Q. Which are present in MSN's form S?

12:06:29 10 A. All of them.

12:06:30 11 Q. Which, if any, of these structural features are  
12:06:34 12 present in the other purported forms discussed by Dr. Steed?

12:06:37 13 A. Well, to the extent that they're crystalline  
12:06:40 14 cabozantinib (L)-malate or malate broadly, then they're  
12:06:44 15 present.

12:06:45 16 Q. So just to recap: What is your opinion regarding  
12:06:47 17 whether the inventors possessed the full scope of the claims  
12:06:50 18 under Dr. Steed's interpretation?

12:06:52 19 A. My opinion is that they did.

12:06:54 20 Q. Let's shift topics now and move to obviousness-type  
12:06:57 21 double patenting.

12:06:58 22 Now, have you formed an opinion on whether the  
12:07:00 23 asserted claims are patentably distinct over Claim 5 of --  
12:07:04 24 over -- of the '473 compound patent?

12:07:07 25 A. Yes, I did.

Trout - Direct

12:07:07 1 Q. And what is your opinion?

12:07:08 2 A. My opinion is that they are, indeed, patentably  
12:07:11 3 distinct over Claim 5 of the '473 patent.

12:07:15 4 MR. PRUSSIA: Let's please have PDX-19.

12:07:15 5 BY MR. PRUSSIA:

12:07:17 6 Q. At a high level, what are the reasons for your  
12:07:19 7 opinion?

12:07:19 8 A. Well, first of all, there are very significant  
12:07:21 9 differences between claims and there's no motivation to  
12:07:27 10 pursue the salt based on the prior art. Even if there were,  
12:07:31 11 there was no motivation to include malic acid in the salt  
12:07:35 12 screen based on the prior art.

12:07:36 13 Even if the skilled person were to pursue a salt  
12:07:41 14 screen with malic acid, there was no reasonable expectation  
12:07:43 15 of success.

12:07:44 16 And then finally, objective evidence confirms  
12:07:47 17 non-obviousness.

12:07:48 18 Q. So, let's take each one of these in turn and start  
12:07:51 19 with your first reasoning for that.

12:07:54 20 MR. PRUSSIA: And we'll pull up PTX-252. It's  
12:07:58 21 Tab 6 in the binder.

12:07:58 22 BY MR. PRUSSIA:

12:07:58 23 Q. And what is this document?

12:08:01 24 A. This document is the '473 patent.

12:08:07 25 Q. What is the issue date of the '473 patent?

Trout - Direct

12:08:09 1 A. That's August 25th, 2009.

12:08:13 2 Q. Have you offered an opinion on whether the '473

12:08:16 3 patent is prior art to the asserted claims?

12:08:18 4 A. Yes, I have.

12:08:18 5 Q. What is your opinion?

12:08:19 6 A. It is not prior art.

12:08:21 7 Q. And in your opinion, when were the asserted claims

12:08:25 8 reduced to practice?

12:08:25 9 A. Well, we heard from Dr. Shah yesterday they were

12:08:29 10 reduced to practice a lot earlier, I believe 2004.

12:08:33 11 Q. And what is the priority date of the asserted claims?

12:08:35 12 A. The priority date of the asserted claims is

12:08:39 13 January 16th, 2009.

12:08:41 14 Q. Now, let's look at Claim 5 itself.

12:08:43 15 MR. PRUSSIA: If we turn to Column 412 of the

12:08:48 16 '473 patent.

12:08:48 17 BY MR. PRUSSIA:

12:08:49 18 Q. What is Claim 5 directed to?

12:08:50 19 A. Well, it's directed to cabozantinib, that's, again,

12:08:54 20 the molecular structure that is on the screen. That's the

12:08:59 21 free base or a pharmaceutically acceptable salt thereof.

12:09:03 22 Q. Does Claim 5 require a pharmaceutically acceptable

12:09:07 23 salt?

12:09:07 24 A. No.

12:09:08 25 MR. PRUSSIA: Let's have PDX 20.

Trout - Direct

12:09:08 1 BY MR. PRUSSIA:

12:09:11 2 Q. What are the differences between Claim 5 of the  
12:09:15 3 '473 patent and the asserted claims?

12:09:17 4 A. Well, quite a few differences and forgive me --  
12:09:20 5 forgive us, Your Honor, for including a whole bunch of  
12:09:24 6 different colors.

12:09:24 7 But just to point out the differences here, in  
12:09:27 8 yellow there's the malate salt, (L) or (D) for example. In  
12:09:33 9 red, pharmaceutical composition. Neither of those, I should  
12:09:38 10 make clear, are in Claim 5 of the '473.

12:09:41 11 Crystalline, in blue, is also not in Claim 5 of  
12:09:45 12 the '473. And the method of treating cancer where said  
12:09:50 13 cancer is kidney cancer, that's in green in the asserted  
12:09:54 14 malate crystalline salt patents, also is not in Claim 5 of  
12:09:58 15 the '473.

12:10:00 16 Q. So just on a pure comparison of the claims, in your  
12:10:04 17 opinion, are the claims of the crystalline malate salt  
12:10:06 18 patents patentably distinct from Claim 5?

12:10:09 19 A. Yes.

12:10:10 20 Q. Now, let's focus on the disclosures of the  
12:10:13 21 '473 patent specification. What, if any, cabozantinib salts  
12:10:17 22 are exemplified in the '473 patent?

12:10:19 23 A. Well, there's a -- oh, cabozantinib salts? None.

12:10:25 24 Q. So what, if any, information is disclosed in the  
12:10:29 25 '473 patent regarding a (L)-malate salt of cabozantinib?

Trout - Direct

12:10:30 1 A. Nothing.

12:10:32 2 Q. What, if any, information is disclosed in the  
12:10:36 3 '473 patent regarding a (D)-malate salt of cabozantinib?

12:10:38 4 A. Nothing.

12:10:39 5 Q. What crystalline cabozantinib is exemplified  
12:10:43 6 in the '473 patent?

12:10:44 7 A. None.

12:10:45 8 Q. What, if any, information does the '473 patent  
12:10:48 9 disclose about crystalline polymorphs of any crystalline  
12:10:53 10 cabozantinib salt?

12:10:53 11 A. Nothing.

12:10:55 12 Q. What, if any, pharmaceutical compositions of  
12:10:58 13 cabozantinib are exemplified in the '473 patent?

12:11:01 14 A. None.

12:11:02 15 Q. What, if any, methods of treating kidney cancer with  
12:11:04 16 cabozantinib are exemplified in the '473 patent?

12:11:07 17 A. None.

12:11:09 18 Q. Let's turn back to Claim 5 itself. And now I want to  
12:11:13 19 focus on the language regarding a pharmaceutically  
12:11:15 20 acceptable salt.

12:11:17 21 A. Okay.

12:11:17 22 Q. What information is disclosed in the '473 patent  
12:11:21 23 regarding a pharmaceutically acceptable salt?

12:11:22 24 A. Well, there's a definition of pharmaceutically  
12:11:26 25 acceptable salts or particular acids that could be used to

Trout - Direct

12:11:30 1 form pharmaceutically acceptable salts in the patent.

12:11:33 2 MR. PRUSSIA: Let's turn to Column 270, Lines 15  
12:11:37 3 through 25.

12:11:37 4 BY MR. PRUSSIA:

12:11:42 5 Q. What is listed -- what is identified at this portion  
12:11:44 6 of the '473 patent specification?

12:11:46 7 A. Well, starting at Line 15 -- yeah, and I think we can  
12:11:52 8 just start at Line 15 there -- "pharmaceutically acceptable  
12:11:56 9 acid addition salt," that's under the definition section in  
12:12:01 10 the patent; that's in quotes. And so, this is the  
12:12:04 11 definition of pharmaceutically acceptable acid addition  
12:12:07 12 salts.

12:12:08 13 Q. And how many acids are listed by name in this  
12:12:11 14 definition?

12:12:11 15 A. Twenty-four.

12:12:15 16 MR. PRUSSIA: Can we write 24 on the screen?

12:12:15 17 BY MR. PRUSSIA:

12:12:17 18 Q. Now, does the '473 patent identify malic acid as a  
12:12:24 19 pharmaceutically acceptable acid addition salt?

12:12:27 20 A. No, it's not identified in this list.

12:12:30 21 Q. And what acids would -- a skilled person looking at  
12:12:32 22 the '473 patent specification, what would they have started  
12:12:37 23 with as a potential counterion for cabozantinib?

12:12:40 24 A. Well, the acids that are identified in this list.

12:12:44 25 Q. Now, what is your response -- you heard Dr. Steed's



Trout - Direct

12:12:49 1 testimony about "the words at the end" and the like?

12:12:52 2 A. Yes.

12:12:52 3 Q. What is your response to that testimony?

12:12:54 4 A. Well, Dr. Steed said "and the like" might mean 50  
12:12:58 5 other acids. We heard today from the Bighley reference that  
12:13:02 6 there were 113. Of course, some of these were on that list,  
12:13:06 7 but all in all there are over 113. I think that would be  
12:13:10 8 the reasonable way of thinking of "and the like."

12:13:13 9 Q. So, would a skilled person reading Claim 5 of the  
12:13:20 10 '473 patent and its definition of a pharmaceutically  
12:13:22 11 acceptable salt, would that person have a immediately  
12:13:26 12 envisioned cabozantinib malate salt from that genus?

12:13:29 13 A. No.

12:13:30 14 Q. And what are the reasons for that?

12:13:32 15 A. Well, again, the genus is very large, over 113, at  
12:13:35 16 least, potential salts.

12:13:38 17 Q. Now, you just heard Dr. Koleng's testimony about 113  
12:13:42 18 pharmaceutically acceptable anionic salts; right?

12:13:45 19 A. Correct.

12:13:46 20 Q. Does that reflect the entire genus of  
12:13:48 21 pharmaceutically acceptable salts that were known as of the  
12:13:51 22 priority date?

12:13:51 23 A. No, that was just from that one reference. There are  
12:13:54 24 additional ones.

12:13:56 25 MR. PRUSSIA: Let's have PDX 21, please. And

Trout - Direct

12:13:58 1 turn to your opinions regarding motivation to pursue a salt.

12:13:58 2 BY MR. PRUSSIA:

12:14:02 3 Q. Now, first, what -- when you were here yesterday,

12:14:05 4 what opinions did you hear from Dr. Steed regarding a

12:14:08 5 motivation to form a salt?

12:14:10 6 A. Frankly, I don't recall hearing any opinions. He had

12:14:16 7 mentioned solubility, but I wasn't sure even if that was the

12:14:20 8 motivation. But that was the closest that he mentioned.

12:14:23 9 MR. PRUSSIA: Can we have PDX-22, please. And

12:14:25 10 let's turn to your opinions on this point.

12:14:25 11 BY MR. PRUSSIA:

12:14:28 12 Q. At a high level, what are the reasons that a skilled

12:14:30 13 person would not have been motivated to pursue a salt?

12:14:32 14 A. Well, overall, first of all, there were no reported

12:14:36 15 problems with cabozantinib in the prior art. Even if one

12:14:41 16 were to focus in on solubility, solubility is not

12:14:45 17 determinative of oral bioavailability. And even if one

12:14:49 18 wanted to improve solubility, there were multiple methods to

12:14:52 19 improve solubility.

12:14:54 20 Q. So as of the priority date, what, if any, information

12:14:57 21 was disclosed in the prior art regarding the reasons to form

12:15:00 22 a salt with cabozantinib?

12:15:01 23 A. Nothing.

12:15:02 24 Q. Does the '473 disclose anything regarding the reasons

12:15:06 25 to form a salt with cabozantinib?

Trout - Direct

12:15:07 1 A. No.

12:15:09 2 Q. As of the priority date, what, if anything, was known  
12:15:11 3 about cabozantinib's bioavailability?

12:15:13 4 A. Nothing.

12:15:15 5 Q. As of the priority date, what, if anything, was known  
12:15:17 6 about cabozantinib's solubility?

12:15:19 7 A. Nothing.

12:15:20 8 Q. Does the '473 disclose anything about cabozantinib's  
12:15:24 9 bioavailability or its solubility?

12:15:26 10 A. No.

12:15:27 11 MR. PRUSSIA: Let's have PDX-23, please.

12:15:27 12 BY MR. PRUSSIA:

12:15:30 13 Q. What is your second reason that a skilled person  
12:15:32 14 would not have been motivated to pursue a salt of  
12:15:35 15 cabozantinib?

12:15:35 16 A. Well, even if one did want to focus on solubility,  
12:15:40 17 solubility itself is not determinative of oral  
12:15:43 18 bioavailability.

12:15:44 19 Q. And just taking a step back, what are the reasons  
12:15:47 20 that oral bioavailability -- what's the reason that it's  
12:15:49 21 relevant to your opinion?

12:15:50 22 A. Well, it's quite relevant. This is an oral drug, so  
12:15:55 23 it would be taken through the mouth into the GI system and  
12:15:58 24 then absorbed into the body. And the degree to which it's  
12:16:02 25 absorbed and then can reach the therapeutic site is its

Trout - Direct

12:16:05 1 bioavailability.

12:16:07 2 MR. PRUSSIA: And if we could have PTX-625,

12:16:10 3 Tab 16 in the binders.

12:16:10 4 BY MR. PRUSSIA:

12:16:11 5 Q. What is this document?

12:16:12 6 A. This is the Takagi reference.

12:16:15 7 Q. And what is the title?

12:16:16 8 A. Title is "A Provisional Biopharmaceutical  
12:16:20 9 Classification of the Top 200 Oral Drug Products in the  
12:16:24 10 United States, Great Britain, Spain, and Japan."

12:16:28 11 Q. And what is the date?

12:16:29 12 A. The date is February 21st, 2006.

12:16:33 13 MR. PRUSSIA: And if we turn to Figure 2.

12:16:35 14 BY MR. PRUSSIA:

12:16:35 15 Q. What does this chart disclose to a person of skill as  
12:16:41 16 of the priority date?

12:16:41 17 A. This is a histogram, and you can see in the Y axis,  
12:16:47 18 it's percentage of immediate-release oral drugs. So those  
12:16:53 19 are the relevant drugs that we're talking about here. So it  
12:16:55 20 goes from 0 to about 45 percent. On the left side is the  
12:17:01 21 categories. The different colors just mean the different  
12:17:03 22 countries or jurisdictions. It shows very soluble.

12:17:07 23 And then at the end, not available. So that's  
12:17:10 24 not so important here. But the far end -- or sorry, one  
12:17:14 25 next to the far end, practically insoluble, is the lowest

Trout - Direct

12:17:19 1 category. And one can see that the practically insoluble,  
12:17:24 2 on average, is about 40 percent of all immediate-release  
12:17:28 3 oral drugs, or at least the top ones.

12:17:31 4 Q. So can a compound with poor water solubility  
12:17:33 5 nonetheless be bioavailable.

12:17:35 6 A. Yes.

12:17:36 7 Q. If you turn to PDX-24.

12:17:39 8 At a high level, what are the reasons that a  
12:17:41 9 compound with poor water solubility could nonetheless still  
12:17:44 10 have sufficient bioavailability?

12:17:45 11 A. Well, as I've been saying, poor water or aqueous  
12:17:50 12 solubility is not determinative of bio -- oral  
12:17:53 13 bioavailability. There's also potency, permeability, and  
12:17:58 14 solubility in bio-relevant media.

12:18:01 15 Q. And what's known today about the role that potency  
12:18:03 16 plays in the bioavailability of cabozantinib?

12:18:05 17 A. Well, as Dr. Shah testified yesterday, it turns out  
12:18:09 18 that cabozantinib has high potency.

12:18:11 19 Q. What is known today about the role that permeability  
12:18:15 20 plays in the oral bioavailability of cabozantinib?

12:18:17 21 A. Well, again, as we heard from Dr. Shah yesterday,  
12:18:21 22 cabozantinib is highly -- or is -- is absorbed very well, so  
12:18:27 23 it's considered highly permeable.

12:18:29 24 Q. What does solubility in bio-relevant media refer to?

12:18:33 25 A. So we've been talking earlier about aqueous

Trout - Direct

12:18:36 1 solubility. So, solubility just in water, per se. But  
12:18:40 2 solubility in bio-relevant media would be in media that's  
12:18:45 3 made to mimic various kind of places in the body. For  
12:18:49 4 example, simulated stomach fluid and also simulated  
12:18:53 5 intestinal fluid.

12:18:55 6 Q. So, to be clear, though, as of the priority date, was  
12:18:57 7 there any information in about cabozantinib's solubility,  
12:19:01 8 its permeability, or its in vivo potency?

12:19:04 9 A. No.

12:19:04 10 Q. And were you here -- again, you heard Dr. Steed  
12:19:06 11 testify that a skilled person could have identified the  
12:19:10 12 water solubility of cabozantinib experimentally?

12:19:13 13 A. Yes.

12:19:14 14 Q. But I think he said they wouldn't go beyond that, do  
12:19:18 15 you remember that?

12:19:18 16 A. Right.

12:19:18 17 Q. Just focusing on whether, if that is correct, that a  
12:19:22 18 skilled person could have experimentally identified the  
12:19:26 19 water solubility, in your opinion, would that POSA have  
12:19:29 20 continued to -- continued to experimentally identify the in  
12:19:36 21 vivo potency, the permeability, and the solubility and  
12:19:39 22 bio-relevant media of cabozantinib?

12:19:41 23 A. They could have.

12:19:42 24 Q. And if that skilled person did so, what would -- what  
12:19:46 25 would they have learned with respect to the need to form a

Trout - Direct

12:19:49 1 salt with cabozantinib?

12:19:50 2 A. Well, again, under that assumption, as we now know  
12:19:54 3 after the fact, that there wasn't an issue actually with  
12:19:59 4 solubility, per se.

12:20:01 5 MR. PRUSSIA: Let's turn to PDX-25.

12:20:01 6 BY MR. PRUSSIA:

12:20:03 7 Q. What is your third reason that a skilled person would  
12:20:05 8 not have been motivated to pursue a salt of cabozantinib?

12:20:08 9 A. Well, even if the skilled person did want to improve  
12:20:12 10 solubility for cabozantinib or another drug, there were  
12:20:17 11 multiple methods to improve solubility.

12:20:20 12 Q. And generally, as of the priority date, what sorts of  
12:20:22 13 methods existed to do so?

12:20:23 14 A. Well, again, Dr. Koleng testified just a little while  
12:20:27 15 ago, so I won't go through all of them again, but one is,  
12:20:31 16 for example, to make it into amorphous material. Another is  
12:20:35 17 to try to reduce particle size, if you wanted to keep it in  
12:20:38 18 crystalline, for example.

12:20:40 19 MR. PRUSSIA: So, let's shift gears and move to  
12:20:42 20 PDX-26.

12:20:42 21 BY MR. PRUSSIA:

12:20:44 22 Q. What is the next reason for your opinion that there  
12:20:47 23 is no obviousness-type double patenting?

12:20:49 24 A. Well, even if one did want to pursue a salt, there  
12:20:52 25 was no motivation to include malic acid in the salt screen.

Trout - Direct

12:20:55 1 MR. PRUSSIA: And if we turn to PDX-27.

12:20:57 2 BY MR. PRUSSIA:

12:20:57 3 Q. How do Dr. Koleng's opinions relate to your opinion  
12:21:01 4 on whether a skilled person would have included malic acid  
12:21:03 5 in a salt screen?

12:21:04 6 A. Well, again, these are Dr. Koleng's opinions just  
12:21:07 7 from a little while ago. I won't repeat them. But I would  
12:21:10 8 agree with those opinions.

12:21:12 9 MR. PRUSSIA: And if we go to PDX-28.

12:21:14 10 BY MR. PRUSSIA:

12:21:14 11 Q. Do you have additional reasons -- strike that.

12:21:18 12 Do you have additional responses to Dr. Steed's  
12:21:20 13 opinions regarding use of malic acid?

12:21:21 14 A. Yes. The Rule-of-2 we've heard about is just one  
12:21:26 15 guideline. It's also not an absolute rule. And,  
12:21:31 16 furthermore, properties of malic acid would not have said --  
12:21:35 17 would not have led the POSA to seek malate salts.

12:21:38 18 Q. Let's focus on the first one first. What's your  
12:21:40 19 opinion regarding Dr. Steed's reliance on the Rule-of-2?

12:21:43 20 A. Well, I think Dr. Steed himself said that it's a  
12:21:47 21 starting point or it's a starting point for a scale. So,  
12:21:52 22 Rule-of-2 is a guideline. There are other rules.

12:21:56 23 Q. You mentioned there are other rules. What is -- you  
12:21:59 24 heard some discussion yesterday about the Rule-of-3. Were  
12:22:01 25 you familiar with that?



Trout - Direct

12:22:01 1 A. I did, Counsel, and I was familiar with that. Yes.

12:22:06 2 Q. And if a skilled person would have followed the

12:22:11 3 Rule-of-3, what conclusions would that person have reached

12:22:14 4 regarding malic acid as a potential counterion for

12:22:17 5 cabozantinib?

12:22:17 6 A. Well, I think you showed yesterday that the skilled

12:22:20 7 person following the Rule-of-3, again, just another

12:22:24 8 guideline. If the person did follow that absolutely, malic

12:22:28 9 acid would have been excluded.

12:22:30 10 Q. Just to be clear, though, in your opinion, would a

12:22:32 11 person of skill have been motivated to follow either

12:22:35 12 Rule-of-2 or a Rule-of-3 in identifying counterions to

12:22:39 13 potentially pair with cabozantinib in a salt screen?

12:22:41 14 A. No, those are guidelines. The skilled person

12:22:45 15 certainly would have taken them into account, but they would

12:22:47 16 not have been determinative of the choice of potential

12:22:50 17 counterions.

12:22:51 18 MR. PRUSSIA: Let's have PDX-29, please.

12:22:51 19 BY MR. PRUSSIA:

12:22:55 20 Q. How do Dr. Koleng's opinions relate -- relate to

12:22:58 21 yours regarding the properties of malic acid?

12:23:00 22 A. Well, again, malic acid, even if one were to pursue

12:23:06 23 the salt screen, had some properties that would have made it

12:23:09 24 undesirable. Dr. Koleng just talked about the weak acidity

12:23:13 25 and the heavy molecular weight. Those would have made it

Trout - Direct

12:23:16 1 undesirable.

12:23:17 2 In addition to that, malic acid actually has two  
12:23:20 3 acid groups so it's doubly ionizable. That can create  
12:23:25 4 complexity and would make it less favorable. In addition to  
12:23:29 5 that, it's subject to pseudodimerism so two molecules of  
12:23:34 6 malic acid could actually react to each other to form one  
12:23:36 7 larger molecule which would have also turned away the  
12:23:40 8 skilled person from malic acid.

12:23:42 9 MR. PRUSSIA: If I could have DTX Steed 26,  
12:23:46 10 please.

12:23:46 11 BY MR. PRUSSIA:

12:23:47 12 Q. Do you recall Dr. Steed's testimony regarding how  
12:23:48 13 hydrogen bonds would have informed salt selection for a  
12:23:52 14 skilled artisan?

12:23:53 15 A. I do.

12:23:53 16 Q. Do you agree that the potential for an eight atom  
12:23:56 17 hydrogen-bonded ring would have led a person of skill to  
12:23:59 18 select malic acid in a salt screen?

12:24:01 19 A. No, and Dr. Steed didn't give any reference for this.  
12:24:04 20 I presume he made it himself, but as far as I can tell, it's  
12:24:08 21 not based on data. And at any rate it's retrospective. It  
12:24:12 22 wouldn't have been known ahead of time.

12:24:14 23 Q. And if Dr. Steed is correct about this -- this  
12:24:18 24 rationale, what would it do to some of the status of what --  
12:24:22 25 strike that.

Trout - Direct

12:24:22 1 If Dr. Steed's theory with respect to hydrogen  
12:24:26 2 binding and its role in identifying counterions were  
12:24:28 3 correct, what would it do -- what would be the result for  
12:24:30 4 the -- as the status of some of the more commonly used  
12:24:34 5 counterions for -- as potential salt formers?

12:24:37 6 A. Well, the more commonly used ones could also form  
12:24:40 7 such structures, just an acid group that Dr. Steed has  
12:24:43 8 there. Maybe I'll point it out to the Court. This is just  
12:24:46 9 a general acid group, so any organic acid could form this  
12:24:50 10 making this assumption.

12:24:53 11 MR. PRUSSIA: Now, let's turn to PDX-32, please,  
12:24:56 12 and move to your opinions regarding expectation of success.

12:24:56 13 BY MR. PRUSSIA:

12:24:59 14 Q. At a high level what's your basis for why a skilled  
12:25:01 15 person would not have had a reasonable expectation of  
12:25:03 16 success?

12:25:04 17 A. Well, there's no expectation of salt formation as  
12:25:07 18 such or isolation of salts. There's no expectation of  
12:25:10 19 crystalline salt formation even if the skilled person could  
12:25:14 20 form a salt. And even if a skilled person formed  
12:25:18 21 crystalline salt of cabozantinib (L)-malate, there would be  
12:25:21 22 no expectation that that salt would have properties suitable  
12:25:25 23 for pharmaceutical development.

12:25:27 24 MR. PRUSSIA: And if we have PDX-33.

12:25:27 25 BY MR. PRUSSIA:

Trout - Direct

12:25:29 1 Q. Focusing on your first point, how do Dr. Koleng's  
12:25:33 2 opinions relate to yours on reasonable expectation of  
12:25:35 3 success?

12:25:36 4 A. Well, I think Dr. Koleng said it quite well  
12:25:38 5 explaining the complexity of salt formation and Your Honor  
12:25:42 6 already saw that. I won't go through it again.

12:25:44 7 MR. PRUSSIA: If we move to PDX-34 to your  
12:25:47 8 second point.

12:25:47 9 BY MR. PRUSSIA:

12:25:47 10 Q. If the skilled person had chosen to perform a salt  
12:25:50 11 screen on cabozantinib. What, if any, expectations would  
12:25:52 12 they have had for obtaining a crystalline cabozantinib  
12:25:56 13 malate salt?

12:25:56 14 A. There wouldn't have been an expectation. Could have  
12:26:00 15 been amorphous, or oily or not crystalline.

12:26:03 16 Q. And generally can you say more about what your  
12:26:05 17 reasoning is for why a person of skill would not have had an  
12:26:08 18 expectation about obtaining crystalline material?

12:26:11 19 A. Yes. Because it's not predictive.

12:26:13 20 Q. And do you recall Dr. Steed's testimony regarding the  
12:26:16 21 Tong Rule-of-2 as providing a person of skill with such  
12:26:19 22 expectation?

12:26:20 23 A. Yes.

12:26:21 24 Q. Do you agree with him?

12:26:22 25 A. No. I think --

Trout - Direct

12:26:23 1 Q. What are the reasons?

12:26:24 2 A. Oh, sorry.

12:26:25 3 Q. It's okay.

12:26:26 4 A. Again, it's -- thank you, counsel.

12:26:28 5 It's one guideline that could be used, and again  
12:26:32 6 as you asked Dr. Steed about this yesterday in the Tong  
12:26:36 7 paper itself, two of the six examples didn't end up forming  
12:26:41 8 crystalline salt.

12:26:43 9 MR. PRUSSIA: If we can have PDX-35.

12:26:43 10 BY MR. PRUSSIA:

12:26:45 11 Q. What is your third reason for why a skilled artisan  
12:26:47 12 would not have had a reasonable expectation of success?

12:26:50 13 A. Well, even if the skilled person did form a  
12:26:52 14 crystalline salt, there was no expectation that the  
12:26:55 15 properties would be suitable for pharmaceutical development.  
12:26:58 16 One couldn't have predicted those properties in advance.

12:27:01 17 MR. PRUSSIA: If you go to PDX-36.

12:27:01 18 BY MR. PRUSSIA:

12:27:03 19 Q. What properties go into identifying the best salt  
12:27:06 20 from the salt screen?

12:27:06 21 A. Well, just a few key properties are the ease of  
12:27:11 22 formation. It's important for manufacturability.  
12:27:15 23 Solubility, we've been talking about. Still important.  
12:27:19 24 Yield. Stability. Hygroscopicity. Flowability. The type  
12:27:24 25 of drug product. Dosage form, for example, tablet. And the

Trout - Direct

12:27:28 1 expected dose.

12:27:30 2 MR. PRUSSIA: If we could please go to PTX-327.

12:27:34 3 It's Tab 10 in the binders. Please identify this reference  
12:27:37 4 for the Court.

12:27:37 5 BY MR. PRUSSIA:

12:27:37 6 Q. Please identify this reference article.

12:27:37 7 A. This is the Berge article -- sorry, Counsel, which  
12:27:40 8 tab did you say it was?

12:27:42 9 Q. Tab 10 in the binders.

12:27:42 10 A. Got it. Thank you.

12:27:52 11 Q. And sorry. I don't know.

12:27:54 12 A. I'm there. Yes.

12:27:55 13 Q. Okay. And what does what is the date of this  
12:27:58 14 reference?

12:27:59 15 A. It's 1977. January 1977.

12:28:02 16 Q. And if we go to the first full paragraph on under  
12:28:07 17 the -- yeah, right there.

12:28:09 18 What does Berge disclose about choosing the  
12:28:13 19 appropriate salts?

12:28:13 20 A. Well, just that second sentence there at the bottom,  
12:28:17 21 "choosing the appropriate salts, however, can be a very  
12:28:20 22 difficult task, since each salt imparts unique properties to  
12:28:24 23 the parent compound."

12:28:26 24 Q. How does this disclosure relate to your opinions in  
12:28:28 25 this case?

Trout - Direct

12:28:28 1 A. Well, it's consistent with my opinions.

12:28:31 2 Q. If we turn to the next paragraph and focusing on the  
12:28:34 3 sentence beginning with "unfortunately."

12:28:37 4 A. Okay.

12:28:37 5 Q. What does Berge disclose to a skilled artisan about  
12:28:40 6 salt selection?

12:28:41 7 A. Well, Berge says, "Unfortunately, there is no  
12:28:44 8 reliable way of predicting the influence of a particular  
12:28:48 9 salt species on the behavior of the parent compound."

12:28:52 10 Q. How does this disclosure relate to your opinions in  
12:28:55 11 this case?

12:28:56 12 A. Well, again, it's consistent with what I've been  
12:28:59 13 saying.

12:29:00 14 MR. PRUSSIA: Now, you can pull that down.

12:29:00 15 BY MR. PRUSSIA:

12:29:02 16 Q. You testified earlier that there were more than 113  
12:29:05 17 pharmaceutically acceptable salts that were known as of the  
12:29:08 18 priority date; right?

12:29:08 19 A. Yes.

12:29:09 20 Q. Now, what, if any, information is disclosed in the  
12:29:14 21 '473 patent regarding the desired properties of a  
12:29:16 22 cabozantinib salt?

12:29:16 23 A. Nothing.

12:29:18 24 Q. And as of the priority date, what information was  
12:29:20 25 disclosed regarding the problems that needed to be addressed

Trout - Direct

12:29:23 1 by forming a salt with cabozantinib?

12:29:26 2 A. None.

12:29:27 3 Q. So what information would have been available to  
12:29:29 4 identify which of the entire genus of pharmaceutically  
12:29:32 5 acceptable salts would have resulted in the right salt for  
12:29:35 6 cabozantinib?

12:29:36 7 A. Nothing.

12:29:39 8 MR. PRUSSIA: If we turn to PDX-37, please.

12:29:39 9 BY MR. PRUSSIA:

12:29:42 10 Q. What is your fifth reason for why the claims are not  
12:29:45 11 invalid for obviousness-type double patenting?

12:29:47 12 A. That objective evidence also confirms  
12:29:51 13 non-obviousness.

12:29:51 14 MR. PRUSSIA: And if we go to PDX-38, please.

12:29:51 15 BY MR. PRUSSIA:

12:29:53 16 Q. At a high level what objective indicia did you  
12:29:56 17 consider?

12:29:56 18 A. Well, there are unexpected results technically. That  
12:30:01 19 is, the malate unexpectedly featured the best suite of  
12:30:05 20 properties, as I've been talking about, and that's despite  
12:30:09 21 the undesirable properties of the malate that I just talked  
12:30:12 22 about a little bit earlier.

12:30:14 23 And as we heard from Dr. Shah yesterday,  
12:30:17 24 crystalline cabozantinib malate has surprisingly better  
12:30:20 25 dissolution properties than amorphous cabozantinib malate.



Trout - Direct

12:30:25 1 Q. So starting with your first point, what are the  
12:30:27 2 reasons that it would have been unexpected that the malate  
12:30:29 3 salt would have provided the best suite of properties?

12:30:32 4 A. Well, as I -- as I said, there's no way to predict  
12:30:35 5 what the pharmaceutical properties would be until the salt  
12:30:39 6 is made and characterized. And it turns out that the malate  
12:30:44 7 salt featured the best suite of properties despite the  
12:30:48 8 potential issues with the low acidity, the high molecular  
12:30:52 9 weight, the tendency to form pseudodimerism and also the  
12:30:55 10 fact that it has two acid groups.

12:30:59 11 Q. Focusing on your second point, what is your second  
12:31:02 12 point?

12:31:02 13 A. Well, okay. So, again, that is from Dr. Shah's  
12:31:08 14 testimony yesterday having to do with the fact that it turns  
12:31:11 15 out unexpectedly the crystalline material has better  
12:31:15 16 dissolution properties than the amorphous material.

12:31:17 17 MR. PRUSSIA: If we go to PDX --

12:31:19 18 THE COURT: Mr. Prussia, excuse me a second.  
12:31:21 19 Dr. Trout, the thing you said a minute ago, that malate  
12:31:24 20 features the best suite of properties, that's based on the  
12:31:27 21 salt screen; right?

12:31:28 22 THE WITNESS: That's -- that's -- yes,  
12:31:30 23 Your Honor. It's based on the salt screen as disclosed in  
12:31:32 24 the asserted patents here. Correct. It wouldn't have been  
12:31:36 25 known before that.

Trout - Direct

12:31:36 1 THE COURT: Okay. Right. Okay.

12:31:38 2 Sorry, go ahead.

12:31:40 3 MR. PRUSSIA: That's okay. It's for you,  
12:31:41 4 Your Honor. Any questions you have, please feel free.

12:31:44 5 PTX-225, please.

12:31:44 6 BY MR. PRUSSIA:

12:31:46 7 Q. What is this document?

12:31:47 8 A. That's the Shah declaration that Dr. Shah testified  
12:31:51 9 about yesterday.

12:31:52 10 MR. PRUSSIA: It's Tab 14 in the binders. If we  
12:31:54 11 could turn, please, to Figure 2.

12:31:54 12 BY MR. PRUSSIA:

12:31:59 13 Q. What does this figure show?

12:32:01 14 A. Well, this is a figure -- again, I think the Court  
12:32:06 15 saw this yesterday. So, this is dissolution, percentage  
12:32:11 16 dissolution from zero to a hundred. It goes up a little  
12:32:15 17 farther, but it's basically zero to a hundred as a function  
12:32:18 18 of time in minutes.

12:32:20 19 And you can see the curve with the squares,  
12:32:24 20 zero percent amorphous. In other words, a hundred percent  
12:32:27 21 crystalline. It dissolves very quickly, and in about  
12:32:31 22 15 minutes that's very rapid. And by contrast, with  
12:32:35 23 20 percent amorphous, this lower curve hardly dissolves or  
12:32:40 24 at least a small fraction dissolves even after an hour and a  
12:32:43 25 half.

Trout - Direct

12:32:44 1 Q. And what conclusions did you reach regarding this  
12:32:48 2 data?

12:32:48 3 A. Well, this was unexpected for a couple reasons. One  
12:32:52 4 is that in general, the skilled person would think that the  
12:32:56 5 amorphous material would dissolve more quickly than the  
12:32:59 6 crystalline material. And then, secondly, just the sheer  
12:33:03 7 fact that the crystalline material, even given its low  
12:33:07 8 solubility, dissolves fully within 15 minutes would have  
12:33:11 9 been unexpected.

12:33:12 10 Q. You mentioned low solubility. Did you hear  
12:33:16 11 Dr. Steed's testimony yesterday that a person of skill would  
12:33:18 12 expect that low water solubility will correlate with the  
12:33:21 13 slow dissolution rate?

12:33:22 14 A. Yes.

12:33:23 15 Q. How does that statement from Dr. Steed relate to your  
12:33:26 16 opinions regarding unexpected results?

12:33:27 17 A. Well, that's the second aspect of my opinions on this  
12:33:30 18 figure. Despite the low solubility, it dissolves completely  
12:33:35 19 within 15 minutes. That's very rapid.

12:33:37 20 MR. PRUSSIA: If we go to JTX-5, which is Tab 17  
12:33:40 21 in its binders.

12:33:40 22 BY MR. PRUSSIA:

12:33:41 23 Q. What is this document?

12:33:42 24 A. This is part of a file history.

12:33:47 25 MR. PRUSSIA: And if we go to Page 373 of JTX-5.

Trout - Direct

12:33:47 1 BY MR. PRUSSIA:

12:33:53 2 Q. What is this portion of the prosecution history?

12:33:55 3 A. This is an office action summary.

12:34:00 4 MR. PRUSSIA: If we go to the next page, 374.

12:34:00 5 BY MR. PRUSSIA:

12:34:03 6 Q. How did the examiner respond to the evidence  
12:34:07 7 submitted in the Shah declaration?

12:34:08 8 A. Well, if we look right under the heading -- and thank  
12:34:11 9 you for highlighting that -- "Declaration of Khalid Shah,"  
12:34:14 10 it says, "The declaration of Khalid Shah" -- and I won't  
12:34:18 11 read the legal aspect of it -- "filed March 19, 2021, is  
12:34:24 12 sufficient to overcome the rejection of Claims 16-20 based  
12:34:29 13 upon" -- and then again the legal -- "as being unpatentable  
12:34:32 14 over Bannen in view of Berge."

12:34:36 15 Q. Now, let's focus on that. There's a reference to a  
12:34:39 16 Bannen patent application ending in the Number '928 and a  
12:34:43 17 Berge reference. Do you see that?

12:34:44 18 A. Yes.

12:34:45 19 Q. Are those the same, '928 patent application and the  
12:34:48 20 Berge reference, that Dr. Steed relied upon during his  
12:34:51 21 testimony to the Court?

12:34:52 22 A. Yes.

12:34:52 23 Q. So, what happened after submission of the Shah  
12:34:56 24 declaration during prosecution?

12:34:58 25 A. Well, based on the Shah declaration, the patent

Trout - Direct

12:35:02 1 examiner concluded that that evidence made it sufficient to  
12:35:06 2 overcome the rejection of the claims. In other words,  
12:35:09 3 allowed the claims of the patent.

12:35:10 4 MR. PRUSSIA: Okay. If you could turn to  
12:35:13 5 PTX-421, Tab 15 of the binders.

12:35:13 6 BY MR. PRUSSIA:

12:35:16 7 Q. What is this document?

12:35:17 8 A. Well, this is the cover page of an edited volume.  
12:35:21 9 The relevant chapter that we'll talk about is by Guillory.

12:35:25 10 MR. PRUSSIA: And can we go to that chapter on  
12:35:27 11 Page 3 of the document.

12:35:28 12 BY MR. PRUSSIA:

12:35:30 13 Q. Who is the author?

12:35:31 14 A. Again, Keith Guillory.

12:35:35 15 MR. PRUSSIA: And if we turn to Page 208, under  
12:35:38 16 the section titled, "Methods employed to obtain amorphous  
12:35:42 17 materials."

12:35:42 18 BY MR. PRUSSIA:

12:35:44 19 Q. Focusing on the very bottom of that page, what does  
12:35:48 20 Guillory disclose regarding the relationship between the  
12:35:50 21 dissolution rate of crystalline amorphous solids?

12:35:53 22 A. Well, again, Guillory discloses what the skilled  
12:35:56 23 person would expect. He says, "While crystalline solids  
12:36:00 24 offer the advantages of chemical and thermodynamic  
12:36:04 25 stability, amorphous solids are occasionally preferred

Trout - Direct

12:36:07 1 because they undergo dissolution at a faster rate."

12:36:11 2 Q. Okay. Just a few more questions, Dr. Steed.

12:36:15 3 MR. PRUSSIA: Can we have PDX-39, please.

12:36:17 4 THE WITNESS: Trout.

12:36:17 5 BY MR. PRUSSIA:

12:36:17 6 Q. Oh, Dr. Trout. Sorry about that.

12:36:24 7 What are your opinions on clinical and  
12:36:26 8 commercial success?

12:36:27 9 A. Well, again, the Court's heard this, that Cabometyx  
12:36:32 10 is the commercial or marketed pharmaceutical in which the  
12:36:38 11 cabozantinib -- the crystalline cabozantinib (L)-malate is  
12:36:40 12 incorporated as the API.

12:36:43 13 And as I've read from Dr. George's report and  
12:36:49 14 Mr. Tate's report, it is both a commercial and clinical  
12:36:53 15 success.

12:36:54 16 Q. Now, what is the commercial embodiment of the  
12:36:56 17 asserted crystalline malate salt patents?

12:36:59 18 A. Well, again, that's the Cabometyx. That's the brand  
12:37:03 19 name.

12:37:03 20 Q. And what is the API in Cabometyx?

12:37:05 21 A. Crystalline cabozantinib (L)-malate.

12:37:09 22 Q. What benefits does the crystalline cabozantinib  
12:37:12 23 (L)-malate invention provide?

12:37:14 24 A. Determinative benefits, it allows it to be  
12:37:18 25 manufactured and it allows it to be formulated or developed

Trout - Direct

12:37:22 1 into a formulation that's stable and safe and effective for  
12:37:26 2 patients.

12:37:28 3 MR. PRUSSIA: Thank you, Dr. Trout.

12:37:29 4 Your Honor, Plaintiffs would proffer the  
12:37:30 5 following exhibits: JTX-1, JTX-2, JTX-3, JTX-5, 6, 7, 9,  
12:37:41 6 10. PTX-283, 225, 252, 258, 327, 421, 625, 774, and 783.

12:38:00 7 And with that, I pass the witness.

12:38:02 8 MR. LOMBARDI: No objections to any of them.

12:38:03 9 THE COURT: All right. Well, why don't we admit  
12:38:05 10 them without objection.

12:37:32 11 (JTX Exhibit Nos. 1, 2, 3, 5, 6, 7, 9, 10, were  
12:37:32 12 admitted into evidence.)

12:37:32 13 (PTX Exhibit Nos. 225, 252, 258, 283, 327, 421,  
12:37:53 14 625, 774, and 783, were admitted into evidence.)

12:38:06 15 THE COURT: And since I was going to take a  
12:38:08 16 lunch break in five minutes anyhow, why don't we take the  
12:38:11 17 lunch break now and we can have cross-examination when we  
12:38:13 18 return.

12:38:14 19 So, we'll take an hour and we'll start again at,  
12:38:18 20 by that clock, 20 minutes of 2.

12:38:22 21 All right. We'll be in recess.

12:38:25 22 DEPUTY CLERK: All rise.

01:39:52 23 (Recess was taken.)

01:39:52 24 Deputy CLERK: All rise.

01:39:53 25 THE COURT: All right. Let's sit down and

Trout - Cross

01:39:55 1 continue.

01:40:06 2 MR. LOMBARDI: Your Honor, we're taking care of  
01:40:08 3 cross binders right now, if that's okay.

01:40:10 4 THE COURT: It's okay.

01:39:59 5 CROSS-EXAMINATION

01:39:59 6 BY MR. LOMBARDI:

01:41:08 7 Q. Good afternoon, Dr. Trout.

01:41:09 8 A. Good afternoon.

01:41:09 9 Q. I'm George Lombardi. We haven't had a chance to  
01:41:13 10 meet.

01:41:13 11 A. No. Nice to meet you.

01:41:14 12 Q. Nice to meet you.

01:41:15 13 Dr. Trout, you talked a lot about crystalline  
01:41:18 14 salts today; is that right?

01:41:20 15 A. Crystalline salts, yes.

01:41:22 16 Q. Crystalline salts may exist in multiple different  
01:41:26 17 polymorphic forms; is that right?

01:41:28 18 A. Yes.

01:41:29 19 Q. It is important in the pharmaceutical industry to  
01:41:33 20 identify and isolate different polymorphs of a crystalline  
01:41:38 21 salt; true?

01:41:42 22 A. Broadly speaking, true.

01:41:44 23 Q. This is because the fact that significant differences  
01:41:48 24 in chemical and physical characteristics may arise with  
01:41:52 25 changes in crystalline form; true?



Trout - Cross

01:41:56 1 A. Yes.

01:41:59 2 Q. These difference can affect the manufacturability,  
01:42:02 3 the performance, and the quality of a drug product; correct?

01:42:08 4 A. Correct. They may.

01:42:11 5 Q. Different crystalline forms of a salt can be  
01:42:14 6 characterized in various ways; is that right?

01:42:18 7 A. Yes.

01:42:19 8 Q. There are various ways that are available this to the  
01:42:25 9 person of skill in the art; correct?

01:42:27 10 A. Yes.

01:42:28 11 Q. One method is XRPD; correct?

01:42:30 12 A. Yes.

01:42:33 13 Q. And you talked about that this morning, that's with  
01:42:35 14 the peaks; right?

01:42:36 15 A. Correct.

01:42:39 16 Q. And there are others, but different forms create  
01:42:43 17 different XRPD -- are they called diffractograms, is that  
01:42:51 18 what you call the result of the next part of the XRPD  
01:42:52 19 analysis?

01:42:52 20 A. Yes, diffractogram is the word.

01:42:54 21 Q. Okay. So different forms -- crystalline forms create  
01:42:57 22 different XRPD diffractograms; correct?

01:43:00 23 A. Generally correct.

01:43:03 24 And, Counsel, it's important that you clarify  
01:43:05 25 crystalline forms because we know without that crystalline

Trout - Cross

01:43:09 1 modifier it has a different meaning.

01:43:12 2 Q. I've been asking you about crystalline forms. You  
01:43:15 3 understand that?

01:43:15 4 A. Yes.

01:43:16 5 Q. Okay. A substance can be identified by its  
01:43:20 6 characteristic XRPD peaks; correct?

01:43:21 7 A. A particular polymorph generally can be, yes.

01:43:27 8 Q. And XRPD gives unique fingerprints of a crystalline  
01:43:31 9 form; correct?

01:43:34 10 A. Again, generally correct.

01:43:35 11 Q. There are other ways to identify crystalline forms or  
01:43:39 12 other ways that can be used to characterize crystalline  
01:43:42 13 forms?

01:43:42 14 A. Yes.

01:43:45 15 Q. Such as thermal characterization. You can do thermal  
01:43:51 16 characterization of a crystalline form?

01:43:53 17 A. Yes.

01:43:53 18 Q. You can do differential scanning calorimetry; is that  
01:43:59 19 right?

01:43:59 20 A. Yes. It's a type of thermal method, as you  
01:44:02 21 mentioned.

01:44:02 22 Q. Moisture absorption is another one you can use?

01:44:06 23 A. Yes.

01:44:06 24 MR. LOMBARDI: Okay. Now, you talked about the  
01:44:09 25 patent here, so let me pull up JTX-1, which is the

Trout - Cross

01:44:09 1 '439 patent.

01:44:09 2 BY MR. LOMBARDI:

01:44:15 3 Q. I'm going to put it on the screen. If you want to  
01:44:18 4 pull it up in front of you, you can. I'm just going to be  
01:44:22 5 showing you the claims, so... If that helps you in  
01:44:24 6 determining what you want to do.

01:44:26 7 A. Okay. If you could just point me to the place in the  
01:44:29 8 binder, too, that would be helpful.

01:44:30 9 Q. It should be the first one in the first binder, I  
01:44:33 10 think.

01:44:34 11 A. Perfect.

01:44:35 12 Q. Got it?

01:44:36 13 A. Yes. Thank you.

01:44:37 14 Q. Okay. So, let's go to where the claims are.

01:44:42 15 A. Oh, I apologize, Counsel. The first one is the '473.  
01:44:46 16 Is that what you...

01:44:47 17 Q. It should -- is that Binder 1?

01:44:52 18 A. Yes.

01:44:58 19 Q. Excuse me. My mistake. It's about halfway through  
01:45:00 20 Volume I. My mistake.

01:45:05 21 Do you have the number? JTX-1. It will say it  
01:45:09 22 on the tab.

01:45:11 23 A. Okay. I've got it now. Thank you.

01:45:22 24 Q. Okay. All right. And -- and I'm back at the claims  
01:45:27 25 at the very end, Doctor.

Trout - Cross

01:45:38 1 Are you there?

01:45:38 2 A. Yes.

01:45:39 3 Q. Okay. And that's what's displayed on the screen;  
01:45:41 4 right?

01:45:42 5 A. Yes.

01:45:43 6 Q. And which claim is at issue here?

01:45:45 7 A. That's claim -- well, the asserted claim is 4.

01:45:50 8 Q. Right. And then it -- it's dependent and it goes  
01:45:53 9 back up, eventually, to 1; is that right?

01:45:55 10 A. Correct.

01:45:55 11 Q. And 1 is where you see the word "crystalline"; right?

01:45:59 12 A. Yes.

01:45:59 13 Q. And that carries through all the way down to Claim 4;  
01:46:02 14 correct?

01:46:03 15 A. Yes.

01:46:06 16 Q. Okay. So, if you -- I want you to -- I'm going to  
01:46:10 17 give you a hypothetical, Doctor. I want you to assume that  
01:46:15 18 Claim 1 says "Wherein said salt is a crystalline form."

01:46:21 19 Okay?

01:46:22 20 A. Okay.

01:46:23 21 Q. Would that cover all forms -- crystalline forms of  
01:46:30 22 the malate salt of the -- is that the (L)-malate salt -- of  
01:46:36 23 the malate salt?

01:46:40 24 A. All polymorphic forms you're asking about?

01:46:43 25 Q. I'm asking if it would cover all forms -- all

Trout - Cross

01:46:46 1 crystalline forms of the malate salt, if it had the word  
01:46:50 2 "form" after crystalline?

01:46:54 3 A. Well, again, under this hypothetical, if you read in  
01:47:00 4 form, it would incorporate at least the forms that we know  
01:47:05 5 today, the N-1, N-2, and the S.

01:47:09 6 Q. Okay. And any forms that arose in the future; right?

01:47:13 7 A. It could. One would have to do the analysis.

01:47:17 8 Q. Okay. Now, if you read it without my hypothetical,  
01:47:22 9 if you read it and it says "Wherein said salt is  
01:47:26 10 crystalline," it will still cover all crystalline forms;  
01:47:32 11 isn't that correct, as you understand it?

01:47:34 12 A. No, Counsel. I don't think that's the way to think  
01:47:39 13 about it. It covers cabozantinib malate, which is  
01:47:44 14 crystalline having the property of crystalline.

01:47:47 15 Q. Does it cover form S?

01:47:48 16 A. Yes.

01:47:51 17 Q. Does it cover form N-1?

01:47:53 18 A. Yes.

01:47:54 19 Q. Does it cover form N-2?

01:47:56 20 A. Yes.

01:47:57 21 Q. Does it cover every form that we know to exist today?

01:47:59 22 A. Yes.

01:48:02 23 Q. Will it cover every form that comes to being in the  
01:48:04 24 future?

01:48:05 25 A. That I'm not sure about.

Trout - Cross

01:48:08 1 Q. Okay. At least it would literally fall within those  
01:48:11 2 words; correct?

01:48:12 3 A. In -- on a high level, yes.

01:48:18 4 Q. Okay. So, the asserted claims in this patent, the  
01:48:25 5 '439 patent, are not limited to forms N-1 and N-2; is that  
01:48:31 6 right?

01:48:31 7 A. Yes.

01:48:37 8 Q. And I think you've said this, but just to be sure:  
01:48:39 9 It covers MSN's form S; correct?

01:48:44 10 A. Yes.

01:48:46 11 Q. All right. Now, we know, as a factual matter,  
01:48:50 12 Doctor, that Exelixis did not invent form S.  
01:48:58 13 We know that as a factual matter; correct?

01:49:00 14 A. That's my understanding. Yes.

01:49:03 15 Q. And we know that the -- the inventors actually did  
01:49:07 16 not -- the Exelixis inventors actually did not invent any  
01:49:10 17 forms beyond N-1 and N-2; correct?

01:49:13 18 A. Speaking of polymorphic forms, that's correct.

01:49:17 19 Q. And if we look at the specification, and you're  
01:49:21 20 welcome to look at it if you want to, I think you'll be able  
01:49:24 21 to answer this without, but there is extensive description  
01:49:28 22 of the forms that were invented by Exelixis in the  
01:49:32 23 specification; correct?

01:49:33 24 A. Again, crystalline or polymorphic forms. Yes.

01:49:38 25 Q. And you used those terms synonymously; right?

## Trout - Cross

01:49:41 1 A. Yes.

01:49:43 2 Q. Okay. And there's an extensive description -- in the  
01:49:48 3 specification, there is a disclosure of techniques used to  
01:49:53 4 identify forms N-1, and N-2; is that right?

01:49:57 5 A. Yes.

01:49:58 6 Q. And then they are, in fact, identified according to  
01:50:02 7 those techniques as N-1 and N-2; correct?

01:50:05 8 A. Correct.

01:50:06 9 Q. And the techniques are XRPD; correct?

01:50:09 10 A. Yes.

01:50:11 11 Q. Thermal characterization; correct?

01:50:13 12 A. Yes.

01:50:14 13 Q. Differential scanning calorimetry; correct?

01:50:17 14 A. Yes.

01:50:18 15 Q. If I say -- am I saying that wrong?

01:50:20 16 A. Differential scanning calorimetry.

01:50:24 17 Q. Calorimetry.

01:50:25 18 A. They're a type of thermal method.

01:50:27 19 Q. And moisture selection; correct?

01:50:29 20 A. Yes.

01:50:29 21 Q. All right. And the specification gives very specific  
01:50:36 22 descriptions of how to prepare N-1 and N-2; is that correct?

01:50:40 23 A. Yes.

01:50:41 24 Q. And there's no question that the inventors have  
01:50:45 25 provided sufficient information to identify N-1 and N-2; is

Trout - Cross

01:50:52 1 that correct?

01:50:52 2 A. Correct.

01:50:53 3 Q. Okay. There's no reference in the specification to  
01:50:56 4 form S; is that correct?

01:50:58 5 A. Correct.

01:50:59 6 Q. There's no reference in the specification to any form  
01:51:03 7 other than N-1 and N-2; correct?

01:51:05 8 A. And again, I -- I apologize, but it's important that  
01:51:08 9 we differentiate salt form from crystalline form. That's  
01:51:13 10 why if you say form --

01:51:14 11 Q. And I'm not meaning to make it -- if I short -- I'll  
01:51:17 12 try not to shortcut it. I'll try not to shortcut it.

01:51:20 13 There's no description in the specification of  
01:51:23 14 any crystalline form other than N-1 and N-2; is that right?

01:51:27 15 A. Correct.

01:51:29 16 Q. And the working examples in the specification relate  
01:51:32 17 only to N-1 and N-2; correct?

01:51:34 18 A. Those -- no, not correct.

01:51:41 19 Q. Okay. Well, the only forms described in example --  
01:51:47 20 working examples of the specification are forms N-1 and N-2,  
01:51:51 21 the only crystalline forms are N-1 and N-2; is that correct?

01:51:54 22 A. With that adjective, correct. Crystalline  
01:51:58 23 polymorphic forms, yes.

01:52:00 24 Q. There are no examples in the specification of how to  
01:52:03 25 make the crystalline forms of cabozantinib (L)-malate other



Trout - Cross

01:52:08 1 than forms N-1 and N-2; correct?

01:52:11 2 A. Crystalline forms, yes.

01:52:14 3 Q. Okay. There is, also -- so you've got forms N-1 and  
01:52:19 4 N-2 described in the specification. My question now is:  
01:52:25 5 There's -- a person of skill in the art would not know  
01:52:29 6 whether other forms -- crystalline forms even existed based  
01:52:35 7 on the disclosure of the specification; isn't that right?

01:52:38 8 A. Yes.

01:52:40 9 Q. Is there is nothing in the specification that enables  
01:52:44 10 the person of skill in the art to predict whether there  
01:52:48 11 would be other forms?

01:52:52 12 A. Correct.

01:52:53 13 Q. A person of skill in the art cannot predict  
01:52:56 14 additional polymorphic forms based on the knowledge of forms  
01:53:01 15 N-1 and N-2; correct?

01:53:03 16 A. That's generally correct. And, I apologize, just to  
01:53:06 17 make the very clear, I'm assuming for all this, when you say  
01:53:08 18 "form" without the proviso, you don't mean salt form, you  
01:53:13 19 mean polymorphic form.

01:53:14 20 Q. I'm talking about crystalline form.

01:53:16 21 A. I know, but it's very important to make sure that we  
01:53:19 22 understand that that's what we're talking about.

01:53:22 23 Q. Okay. And even if one had a crystalline form in  
01:53:35 24 hand, there would be no way to predict in advance what other  
01:53:40 25 crystalline forms of the same compound you might obtain;

Trout - Cross

01:53:43 1 correct?

01:53:44 2 A. Without any information, no.

01:53:47 3 Q. There is just no way a person of skill in the art can  
01:53:51 4 predict which polymorph can be obtained before starting  
01:53:55 5 actual testing; is that right?

01:53:57 6 A. Correct. Not with accurate -- not with great  
01:54:00 7 accuracy, correct.

01:54:01 8 Q. It's only through actual testing that one can  
01:54:05 9 determine whether there are other polymorphic forms; is that  
01:54:10 10 correct?

01:54:10 11 A. Yes.

01:54:12 12 Q. There is no way to know how many polymorphs there  
01:54:16 13 will be based simply on the compound itself; correct?

01:54:20 14 A. I don't think that's fully correct.

01:54:24 15 Q. Okay.

01:54:25 16 A. In broad terms.

01:54:26 17 Q. Okay. There are many factors that can influence  
01:54:36 18 crystallization; correct?

01:54:37 19 A. Yes.

01:54:46 20 Q. Just one moment, Doctor. Oops.

01:54:58 21 There are many factors that can influence  
01:55:00 22 crystallization and that makes the process of identifying a  
01:55:05 23 given crystalline form highly unpredictable; correct?

01:55:10 24 A. Again, you mean in the absence of any information? I  
01:55:16 25 mean, you can identify a sample with the methods we've been

Trout - Cross

01:55:20 1 talking about.

01:55:21 2 Q. You can identify the sample. I'm talking about  
01:55:24 3 identifying other crystalline forms of a compound that you  
01:55:28 4 don't know about yet.

01:55:29 5 I'll give you the question again: There are  
01:55:31 6 many factors that can influence the crystallization process,  
01:55:36 7 and you said yes to that; right?

01:55:38 8 A. Yes.

01:55:39 9 Q. And the process of identifying a given crystalline  
01:55:44 10 form is highly unpredictable; correct?

01:55:47 11 A. Again, if -- if you mean discover a new form, yes.

01:55:54 12 Q. Okay. That's what I mean. Thank you.

01:55:56 13 And there's no way to know how many polymorphs  
01:56:06 14 can be obtained from a particular compound before doing the  
01:56:11 15 actual testing; is that right?

01:56:12 16 A. Well, I don't think that's fully correct.

01:56:17 17 Q. Okay. Why is that not correct?

01:56:19 18 A. Because, as we talked about before, about half of  
01:56:25 19 crystalline materials have only one polymorph. Most of the  
01:56:30 20 others just have a handful. And I think we talked about the  
01:56:33 21 extreme number was 14. So, you may not know the exact  
01:56:37 22 number, but you have a ballpark that it's going to be  
01:56:41 23 relatively small.

01:56:42 24 Q. You can't know until you actually do the testing,  
01:56:45 25 though; correct?

Trout - Cross

01:56:45 1 A. You can't know the results of the test, but again,  
01:56:52 2 you have the ballpark, as I've explained.

01:56:54 3 Q. Okay. There are many factors that affect the  
01:57:05 4 formation of crystalline forms; correct?

01:57:07 5 A. In broad terms, yes.

01:57:11 6 Q. And the some of those factors include the process of  
01:57:20 7 manufacture; right?

01:57:20 8 A. Yes. I mean --

01:57:25 9 Q. Evaporation can effect --

01:57:27 10 A. Okay. Now I understand what you're saying. Yes.

01:57:30 11 Q. Melting can have an effect?

01:57:32 12 A. Again, your question is -- I think you mean process  
01:57:41 13 parameters. I'm --

01:57:44 14 Q. If that makes --

01:57:46 15 A. -- you are --

01:57:46 16 Q. If that makes it easier for you, Doctor.

01:57:47 17 A. Okay.

01:57:49 18 Q. Did you answer that one?

01:57:51 19 Melting can have an effect on the formation of  
01:57:53 20 polymorphs?

01:57:54 21 A. Again, how you do the melting, I think, is what  
01:57:59 22 you're getting at. I wouldn't -- it doesn't quite fit the  
01:58:02 23 way you're asking it.

01:58:03 24 Q. Well, there are a multitude of factors that can  
01:58:06 25 influence the crystallization of a salt; correct?

## Trout - Cross

01:58:08 1 A. Yes.

01:58:09 2 Q. And among those factors are evaporation, melting --

01:58:21 3 A. Again, I would say it that way, Counsel.

01:58:23 4 Q. Well, let's -- well, let me complete the list.

01:58:29 5 Melting. Grinding could have an effect?

01:58:32 6 A. Again, I think you're asking the way you do each of

01:58:35 7 those might have an effect. And the answer is yes, if

01:58:38 8 that's what you're asking.

01:58:39 9 Q. That's what I'm asking.

01:58:40 10 A. Yes.

01:58:41 11 Q. Sublimation?

01:58:42 12 A. The way you do it might have an effect, yes.

01:58:45 13 Q. Okay. They could -- these kinds of methods can have

01:58:48 14 an effect on the formation of polymorphs; correct?

01:58:52 15 A. Yes.

01:58:55 16 Q. And there were a large number of other factors that

01:58:58 17 can influence the crystallization of a salt; correct?

01:59:02 18 A. Yes.

01:59:03 19 Q. Such as concentration of salt in solution?

01:59:06 20 A. Yes.

01:59:08 21 Q. Such as types of solvent used?

01:59:10 22 A. Yes.

01:59:12 23 Q. Such as seeding and agitation?

01:59:15 24 A. Yes.

01:59:16 25 Q. Such as interconversion of solid forms?

Trout - Cross

01:59:18 1 A. I mean, that's not a choice. That's a result.

01:59:24 2 Q. Okay. But all of those things can or -- well, the  
01:59:29 3 presence of additives or impurities can have an effect, too;  
01:59:33 4 right?

01:59:34 5 A. I didn't hear the --

01:59:35 6 Q. The presence of additives and impurities can have an  
01:59:39 7 effect, too; is that right?

01:59:40 8 A. Yes.

01:59:41 9 Q. Okay. Solid forms of compound or salt are affected  
01:59:46 10 by how they are prepared; correct?

01:59:49 11 A. They might be or might not be.

01:59:53 12 Q. Okay. You just don't know until you do it; correct?

01:59:57 13 A. You have to do the experiment, correct. Or have  
02:00:00 14 information already.

02:00:01 15 Q. Okay. Okay.

02:00:04 16 So, Doctor, one moment.

02:00:19 17 In short, many factors can influence the  
02:00:23 18 crystallization of a molecule; correct?

02:00:24 19 A. Yes.

02:00:26 20 Q. And that makes the process of identifying a given  
02:00:30 21 crystalline form highly unpredictable and far from routine;  
02:00:34 22 correct?

02:00:34 23 A. Yes, assuming you don't have information, again.

02:00:41 24 Q. Okay. Now, just to give us more real-world examples  
02:00:51 25 of different polymorphs -- different polymorphs are created

Trout - Cross

02:00:53 1 through different manufacturing processes, we talked about  
02:00:55 2 that; right?

02:00:56 3 A. Yes, for example.

02:00:58 4 Q. And so form N-1 is created one way; is that right?

02:01:03 5 A. Yes.

02:01:04 6 Q. And form N-2 is different in the way it's created;  
02:01:09 7 correct?

02:01:09 8 A. Yes.

02:01:10 9 Q. And form N-1 is actually not equivalent to form N-2;  
02:01:14 10 correct?

02:01:14 11 A. Well, I think, as I've said, they have similar  
02:01:19 12 properties and they can be representative of each other.

02:01:24 13 Q. Okay. But, for instance, N-2 is by -- is not  
02:01:29 14 bioequivalent to N-1; correct?

02:01:34 15 Do you know?

02:01:34 16 A. I'm not sure about that.

02:01:36 17 Q. Okay. Well, do you know that a batch of N-2 is not  
02:01:41 18 bioequivalent to a batch of N-1; do you know one way or the  
02:01:46 19 other?

02:01:46 20 A. I don't know. I know the company decided to pursue  
02:01:52 21 N-2.

02:01:52 22 Q. Okay. And you know that form S, MSN's form S is  
02:01:57 23 manufactured differently than form N-2; correct?

02:02:00 24 A. Correct.

02:02:02 25 Q. And you know that it differs -- well, do you know

## Trout - Cross

02:02:05 1 what part of the manufacturing process is different in that  
02:02:08 2 instance?

02:02:08 3 A. I've read. I don't have them memorized.

02:02:12 4 Q. Okay. But there is a difference which leads to the  
02:02:15 5 difference in the crystalline structure; correct?

02:02:17 6 A. Correct.

02:02:18 7 Q. All right. Now, there are other polymorph forms that  
02:02:24 8 exist beyond form S -- well, you agree that form S is a  
02:02:31 9 different polymorphic form, a different crystalline  
02:02:33 10 structure than N-1 and N-2; correct?

02:02:35 11 A. Yes.

02:02:36 12 Q. Okay. There are other forms beyond that; correct?

02:02:41 13 A. Well, I think I've called into question that, and I  
02:02:46 14 can elaborate more if you'd like. But I think that those  
02:02:50 15 are the three known or bona fide forms.

02:02:54 16 Q. Okay. Well, you have testified, or you were involved  
02:02:59 17 in the first case involving cabozantinib; correct?

02:03:03 18 A. Yes.

02:03:05 19 Q. And in that first case, you provided an expert  
02:03:09 20 report; correct?

02:03:09 21 A. Yes.

02:03:10 22 Q. And in that expert report, you talked about the  
02:03:13 23 number of reported forms of the malate crystalline salt  
02:03:21 24 correct?

02:03:21 25 A. I did talk about, I think, the same ones we've been



Trout - Cross

02:03:24 1 talking about in this trial; correct.

02:03:25 2 Q. And in that expert report, you stated that there --

02:03:31 3 well, why don't we just put this up?

02:03:34 4 MR. LOMBARDI: Let's go to the Cabo rebuttal

02:03:36 5 report on Paragraph 313.

02:03:54 6 THE WITNESS: And, counsel, could you -- it's a

02:03:55 7 little easier for me to read it, if you don't mind.

02:03:58 8 BY MR. LOMBARDI:

02:03:58 9 Q. Okay. Your rebuttal report is going to be, I think,

02:04:00 10 at the back of the second volume.

02:04:01 11 A. Okay. Thank you.

02:04:05 12 Oh, yes.

02:04:06 13 Q. Tell me when you're ready, Doctor.

02:04:28 14 A. I'm ready.

02:04:28 15 Q. Okay. I'm at Paragraph 313. It should be Page 108.

02:04:43 16 A. I'm there.

02:04:44 17 Q. Okay. And you note what -- you were testifying on

02:04:48 18 behalf -- providing expert report on behalf of Exelixis in

02:04:52 19 that case; correct?

02:04:53 20 A. Correct.

02:04:54 21 Q. And about -- one, two, three -- fourth line down, you

02:04:58 22 see, "As Dr. Steed concedes."

02:05:00 23 Do you see that?

02:05:01 24 A. Oh, yes.

02:05:07 25 Q. And it says, "As Dr. Steed concedes, the BMS team

Trout - Cross

02:05:11 1 reports form N-1, N-5 and several others."

02:05:16 2 BMS refers to what?

02:05:17 3 A. Well, that's a company that did a polymorph screen.

02:05:22 4 Q. And the company --

02:05:23 5 A. Oh, Bristol-Myers-Squibb.

02:05:25 6 Q. Thank you.

02:05:26 7 "Further, and as explained above, additional  
02:05:29 8 documents identified in discovery make clear that there are  
02:05:32 9 at least 12 reported forms of the cabozantinib (L)-malate  
02:05:37 10 salt."

02:05:38 11 Do you see that?

02:05:39 12 A. Yes.

02:05:40 13 Q. And then it says, "Form M and form S, that MSN  
02:05:44 14 represents it has created M-1 to M-4 forms and C-2 to C-5  
02:05:50 15 forms in addition to form N-1 and N-2."

02:05:55 16 Do you see that?

02:05:55 17 A. Yes.

02:05:55 18 Q. And then you say, "Thus discovery plainly refutes  
02:05:59 19 Dr. Steed's opinion."

02:06:01 20 Correct?

02:06:02 21 A. That's what's written, yes.

02:06:04 22 Q. Okay. And then on page -- the next paragraph,  
02:06:07 23 paragraph -- or excuse me, two paragraphs down,  
02:06:11 24 Paragraph 315. This will be more towards the top, about --  
02:06:22 25 let's see, again, four lines down.

Trout - Cross

02:06:26 1 Doctor, we'll highlight it. It begins, "As  
02:06:27 2 discussed above."

02:06:30 3 Do you see that?

02:06:30 4 A. Yes.

02:06:31 5 Q. And you said, "As discussed above, there are at least  
02:06:35 6 12 reported forms of the (L)-malate salt: Form M and form S  
02:06:41 7 that MSN represents it has created, M-1 to M-4 forms and C-2  
02:06:46 8 to C-5 forms, in addition to form N-1 and N-2."

02:06:52 9 Do you see that?

02:06:53 10 A. Yes. Yes.

02:06:54 11 Q. And this is what you said in that litigation;  
02:06:57 12 correct?

02:06:57 13 A. Yes. And in this litigation, Dr. Steed also thought  
02:07:01 14 that was the case and I did a deeper analysis, as I  
02:07:05 15 elaborated in my reports, and unfortunately that calls into  
02:07:08 16 question those documents.

02:07:11 17 Q. Okay. Well, Doctor, at this time, it was in  
02:07:16 18 Exelixis' interest -- well, at this time, I mean, at the  
02:07:19 19 time you wrote the report we have on the screen. Got that  
02:07:23 20 time -- time frame; right?

02:07:25 21 A. Yeah. Let me just confirm just to make sure I have  
02:07:29 22 the exact date, but yes, I have the time frame, but let me  
02:07:32 23 just look at the date.

02:07:39 24 Okay. I've got it. Thank you.

02:07:41 25 Q. So, you were involved in the *Cabo I* case, and you

Trout - Cross

02:07:44 1 filed an expert report?

02:07:45 2 A. Correct.

02:07:46 3 Q. And at that time, it was in Exelixis' interest that  
02:07:52 4 you recognized 12 reported forms; is that right?

02:07:56 5 A. Counsel, I'm trying to report the best science I  
02:07:59 6 could. That's what everyone thought at the time, including  
02:08:03 7 Dr. Steed, as of a few months ago. A deeper analysis that I  
02:08:08 8 did calls into question the clarity of that and those  
02:08:12 9 documents.

02:08:13 10 Q. Okay. And so, in this litigation, it's in Exelixis'  
02:08:17 11 best interest for you to say there are a smaller number of  
02:08:21 12 forms; is that right?

02:08:22 13 A. I tried to do the scientific analysis. Exelixis'  
02:08:27 14 interest is their own business. I went through those in  
02:08:31 15 some depth over many pages, and I can demonstrate to you and  
02:08:35 16 the Court why in additional depth these putative forms are  
02:08:40 17 at least not clearly new forms.

02:08:42 18 Q. Now, Doctor, I understand and you -- what you showed  
02:08:46 19 the judge this morning, what you chose to show was form M;  
02:08:50 20 right?

02:08:50 21 A. From Mylan?

02:08:53 22 Yeah, well, there are two form Ms. It's a  
02:08:58 23 little confusing. One was form M from MSN. And one was  
02:09:03 24 form M-1 from Mylan.

02:09:05 25 Q. And it was form M-1 from Mylan that you showed the

Trout - Cross

02:09:08 1 judge this morning; is that right?

02:09:10 2 A. Well, I showed both, but, yes, including M-1,  
02:09:13 3 correct.

02:09:14 4 Q. Okay. All right. Now, in any event, as you agree  
02:09:20 5 that -- well, strike the question.

02:09:24 6 Now, polymorphs -- properties of polymorphs  
02:09:30 7 differ; is that right?

02:09:34 8 A. In general, they -- they can differ. The question  
02:09:37 9 is: Is it significant?

02:09:38 10 Q. Okay. And the physical properties of a crystalline  
02:09:43 11 salt can differ; is that right?

02:09:45 12 A. I'm sorry. Again, you're talking about polymorphs?

02:09:53 13 Q. Yes. Polymorphic forms, crystalline forms.

02:09:57 14 A. Okay.

02:09:57 15 Q. Their properties can differ; right?

02:09:59 16 A. They -- they might differ. They might not  
02:10:02 17 significantly.

02:10:02 18 Q. Okay. Different crystal forms of a particular salt  
02:10:11 19 can have different chemical properties; correct?

02:10:14 20 A. They can. Again, the question is: Are they  
02:10:17 21 significantly different?

02:10:18 22 Q. Okay. Crystalline solids -- and you don't find that  
02:10:22 23 out until you do the testing; right? Whether they're  
02:10:25 24 significantly different or not?

02:10:26 25 A. Yes.

## Trout - Cross

02:10:29 1 Q. You don't find -- you agree? You don't find out  
02:10:32 2 until you do the testing; correct?

02:10:33 3 A. Agreed.

02:10:35 4 Q. Crystalline solids have the same chemical composition  
02:10:38 5 but different crystal structures. And, therefore, different  
02:10:42 6 properties; correct?

02:10:43 7 A. Again, I think I know what you mean, but you're not  
02:10:49 8 using the terminology properly. I think you mean different  
02:10:53 9 crystalline polymorphs. But ask your question as you will.  
02:10:58 10 I'll answer it.

02:10:59 11 Q. Crystalline solids have the same chemical  
02:11:01 12 composition, but different crystalline structures. That  
02:11:05 13 much is right; correct?

02:11:06 14 A. Again, I think to be precise, you're saying different  
02:11:14 15 crystalline polymorphs, not just -- I think that's what you  
02:11:18 16 mean, but...

02:11:18 17 Q. Okay. Crystalline solids --

02:11:20 18 A. Yes.

02:11:21 19 Q. -- can be classified into polymorphs; correct?

02:11:23 20 A. If you -- if you divide them up into polymorphs, yes.

02:11:29 21 Q. And those are forms having the same chemical  
02:11:32 22 composition but different crystal structures; correct?

02:11:35 23 A. Crystalline forms, yes.

02:11:37 24 Q. And, therefore, they can have different densities?

02:11:40 25 A. They can.

Trout - Cross

02:11:41 1 Q. They can have different melting points?

02:11:43 2 A. Yes.

02:11:44 3 Q. They can have different solubilities?

02:11:46 4 A. Yes.

02:11:47 5 Q. And they can differ in other properties as well;  
02:11:49 6 correct?

02:11:50 7 A. They can, yes.

02:11:51 8 Q. They could be different in hygroscopicity; correct?

02:11:55 9 A. They can be.

02:11:56 10 Q. They can be different in solubility; correct?

02:11:59 11 A. Yes.

02:12:00 12 Q. They can be different in stability; correct?

02:12:01 13 A. They can be.

02:12:04 14 Q. They can be different in vapor pressure; correct?

02:12:08 15 A. They can be.

02:12:10 16 Q. They can be different even in color; correct?

02:12:14 17 A. Correct.

02:12:15 18 Q. Changes in a polymorphic form of a pharmaceutical  
02:12:18 19 compound can impact chemical stability?

02:12:22 20 A. Changes, meaning there's a transformation, if that's  
02:12:27 21 the --

02:12:29 22 Q. Changes in the polymorphic form.

02:12:31 23 A. Yes. Yes.

02:12:32 24 Q. Okay. It is true, sir, that in addition to these  
02:12:41 25 differences in polymorphic form affecting those properties,

Trout - Cross

02:12:45 1 the result can be a difference -- it could be variable  
02:12:48 2 potency of a compound.

02:12:50 3 A. That's a possibility. Yes.

02:12:52 4 Q. And by "potency," you mean how strong the compound  
02:12:55 5 is?

02:12:55 6 A. Well, I guess bioavailability perhaps, yes.

02:13:04 7 Q. Okay. Which is important in the pharmaceutical  
02:13:07 8 world; correct?

02:13:07 9 A. Yes.

02:13:08 10 Q. Very important in the pharmaceutical world?

02:13:11 11 A. Yes.

02:13:11 12 Q. And the prior art taught that the range and  
02:13:15 13 combinations of crystal growth conditions are virtually  
02:13:19 14 infinite; isn't that right?

02:13:22 15 A. Yes.

02:13:27 16 Q. And there is no way to guarantee the preparation of  
02:13:31 17 additional polymorphs of a substance, much less the  
02:13:34 18 generation of all of them; correct?

02:13:36 19 A. Could you please repeat that?

02:13:40 20 Q. Well, let me -- you actually wrote that -- you quoted  
02:13:44 21 somebody in your -- in your expert report in the prior case;  
02:13:48 22 correct?

02:13:48 23 A. I just didn't hear the first part of the statement.

02:13:50 24 Q. Okay. Well, let me show it to you.

02:13:54 25 MR. LOMBARDI: Let's go to the rebuttal report



Trout - Cross

02:13:55 1 at Paragraph 277. It's the same report you were looking at  
02:13:59 2 before if you want to look at it.

02:14:00 3 A. Okay.

02:14:15 4 Q. Do you see 277?

02:14:19 5 A. I do. Yes.

02:14:20 6 Q. Okay. And we can just start this at the beginning.  
02:14:28 7 This is your report, and let's make sure that your opinions  
02:14:32 8 are the same today, okay?

02:14:34 9 A. Oh, absolutely correct.

02:14:36 10 Q. "Further, even if a crystalline form is attained,  
02:14:39 11 there was no way at the priority date to predict in advance  
02:14:42 12 what crystalline form (or forms) that compound would  
02:14:45 13 assume."

02:14:47 14 You agree with that today?

02:14:48 15 A. Yes.

02:14:49 16 Q. Okay. "Critically, as explained" -- and then you  
02:14:52 17 have a reference to a section -- "solid forms of a compound  
02:14:57 18 or salt are affected by how they are prepared, which include  
02:15:01 19 factors such as solvents, temperatures, concentration,  
02:15:05 20 agitation, and pH."

02:15:09 21 Do you still have that opinion today?

02:15:10 22 A. Yes.

02:15:11 23 Q. "There is no standard approach, and there was no  
02:15:14 24 teaching in the prior art regarding the parameters to use in  
02:15:17 25 forming an (L)-malate salt of cabozantinib."

Trout - Cross

02:15:22 1 That's still true today?

02:15:24 2 A. Yes.

02:15:25 3 Q. "Without information, there was no way a POSA would  
02:15:29 4 have had any reasonable expectation of which form" -- "solid  
02:15:35 5 form" -- I'm sorry -- "which solid form, if any, would be  
02:15:38 6 obtained, nor any reasonable expectation of preparing the  
02:15:42 7 N-2 crystalline form."

02:15:44 8 Is that your opinion still today?

02:15:45 9 A. Yes.

02:15:47 10 Q. And then as the prior art taught -- and here you  
02:15:51 11 quote. Okay?

02:15:51 12 The range and combinations of crystal growth  
02:15:54 13 structures are virtually infinite and there is no way to  
02:15:58 14 guarantee the preparation of additional polymorphs of a  
02:16:02 15 substance, much less the generation of all of them.

02:16:08 16 Is that still your opinion, today?

02:16:11 17 A. Yes.

02:16:15 18 Q. Now, not every crystalline form or polymorph -- well,  
02:16:22 19 you're using those synonymously; right?

02:16:24 20 A. Yes. Yes.

02:16:25 21 Q. Okay. Can be used in a pharmaceutical composition;  
02:16:29 22 right?

02:16:29 23 A. I mean, it's a very general question. So, yes.

02:16:37 24 Q. Let me make sure -- I might have put a negative in  
02:16:39 25 there. I just want to make sure we're clear.

Trout - Cross

02:16:41 1 It is true that you cannot use every crystalline  
02:16:47 2 form of a particular compound in a pharmaceutical  
02:16:50 3 composition; is that right?

02:16:51 4 A. Oh. Maybe or maybe not, it depends on the situation.

02:16:58 5 Q. And you'd have to do the testing to know; right?

02:17:01 6 A. Yes, if you had no other information.

02:17:03 7 Q. Okay. And the FDA actually requires manufacturers to  
02:17:10 8 provide information about polymorphic forms; correct?

02:17:14 9 A. I mean, there's guidelines but you could say de facto  
02:17:21 10 requirements. Technically, they're guidelines. But yes,  
02:17:24 11 guidelines.

02:17:24 12 Q. And significant differences and -- well, strike the  
02:17:28 13 question.

02:17:28 14 And in the guidelines, they talk about the fact  
02:17:32 15 that the manufacturer must make a determination whether  
02:17:39 16 there are multiple solid state forms; right?

02:17:44 17 You have to do that. You have -- a solid state  
02:17:46 18 form refers to something like crystalline forms; right?

02:17:48 19 A. Correct.

02:17:50 20 Q. Okay. Whether there are multiple solid state forms  
02:17:53 21 and whether these affect the dissolution and bioavailability  
02:17:57 22 of the drug?

02:18:00 23 A. Yes. That's correct. Yes.

02:18:02 24 Q. Okay. And they want you to do that because not every  
02:18:06 25 polymorph will have an effect?

Trout - Cross

02:18:11 1 A. Again, the concern is that might be the case.

02:18:13 2 Q. And you can only know by doing the testing; is that  
02:18:18 3 correct?

02:18:18 4 A. Yes.

02:18:20 5 Q. Okay. Now, there are examples of polymorphs that  
02:18:27 6 worked for pharmaceutical purposes and polymorphs of the  
02:18:31 7 same compound that didn't work; correct?

02:18:34 8 You've talked about this before; right?

02:18:37 9 A. I'm sure I have. And, yes, there are.

02:18:40 10 Q. Okay. And I just ask again: I mean, you understand  
02:18:43 11 that N-1 is -- is not used in a pharmaceutical composition.  
02:18:49 12 Form N-1 from Exelixis; correct?

02:18:50 13 A. That's my understanding. Exelixis commercialized  
02:18:55 14 form N-2, yes.

02:18:56 15 Q. Right. Okay.

02:18:57 16 And so, that's one example of a polymorph for  
02:19:00 17 the same compound where one -- polymorphs of the same  
02:19:04 18 compound where one worked and one didn't work; correct?

02:19:07 19 A. No, I wouldn't say that.

02:19:09 20 Q. Oh, okay. All right. Well, how about -- Norvir is  
02:19:13 21 an example that you've talked about; correct?

02:19:15 22 A. Yes.

02:19:16 23 Q. And Norvir was a situation where one polymorph of a  
02:19:19 24 compound worked for pharmaceutical purposes in a  
02:19:24 25 pharmaceutical composition; right?

## Trout - Cross

02:19:26 1 A. Yes.

02:19:27 2 Q. And another polymorph emerged which did not work; is  
02:19:32 3 that right?

02:19:32 4 A. I think that's right. I'm trying to remember  
02:19:34 5 specifically Norvir, but that sounds right.

02:19:37 6 Q. Okay. Now, form S is, in fact, different than forms  
02:19:46 7 N-1 and N-2 in several ways; isn't that right?

02:19:51 8 A. There are differences and there are similarities.

02:19:56 9 Q. Okay. Form S is hygroscopic?

02:19:59 10 A. It's been characterized as hygroscopic, yes.

02:20:02 11 Q. Form N-2 is not -- I'm sorry. I didn't mean to  
02:20:04 12 interrupt you.

02:20:05 13 A. Sorry. I just wanted to make sure it's clear to the  
02:20:07 14 Court, it's nonhygroscopic enough to be used in MSN's  
02:20:13 15 product.

02:20:15 16 Q. And form N-2 is not hygroscopic; right?

02:20:19 17 A. That's how it's been characterized, correct.

02:20:22 18 Q. Form S has a low melting point; is that correct?

02:20:25 19 A. No, I wouldn't say it that way.

02:20:28 20 Q. Well, it has a -- it has a melting point lower than  
02:20:31 21 186 to 187; correct?

02:20:33 22 A. That's correct.

02:20:35 23 Q. And you would characterize that -- that would be  
02:20:37 24 considered -- well, that would be considered lower than the  
02:20:40 25 form N-1, N-2 melting point; isn't that right?

Trout - Cross

02:20:43 1 A. Well, it has a lower melting point than the form N-1  
02:20:48 2 or N-.2, I think I explicitly didn't say it's a low melting  
02:20:54 3 point.

02:20:54 4 Q. Okay. And you talked about, I think you said, and I  
02:20:59 5 might get the words wrong, but -- correct me if I've got it  
02:21:02 6 wrong, but I think you said that form N-2 is the very best  
02:21:05 7 in terms of stability of the polymorphs, the crystalline  
02:21:09 8 forms of the cabo malate salt; is that right?

02:21:14 9 A. I don't think that's what I said. I think that  
02:21:16 10 overall -- well, first of all, I think I said overall the  
02:21:20 11 crystalline (L)-malate has the best suite or combination of  
02:21:23 12 properties.

02:21:24 13 Q. Okay. And are you aware that Exelixis has said that  
02:21:27 14 form S has a lower stability than N-2, a lesser stability?

02:21:31 15 A. I don't remember the specific document. But if you  
02:21:38 16 say so, I'm sure that's the case. MSN says it's stable  
02:21:42 17 enough to be a product.

02:21:52 18 Q. Just a few questions on your obviousness-type double  
02:21:56 19 patenting. So, I'm changing gears, just so you know.

02:22:00 20 Obviousness-type double patenting now, Doctor.

02:22:03 21 So, the malate salt was known for use in  
02:22:09 22 pharmaceutical compositions as of the priority date in this  
02:22:12 23 case; is that right?

02:22:13 24 A. Again, your question -- I think what you mean is  
02:22:20 25 malic acid, but...

Trout - Cross

02:22:22 1 Q. Well, or the malate salt that results from use of  
02:22:25 2 malic acid.

02:22:26 3 A. There were, as we heard this morning, a small number  
02:22:30 4 of examples in the past, yes.

02:22:31 5 Q. Yeah. (L)-malate salt was known to be a  
02:22:35 6 pharmaceutically acceptable salt as of the early 2000s; is  
02:22:38 7 that right?

02:22:39 8 A. Again, I'm just trying to help you with -- yes, for  
02:22:45 9 specific compounds.

02:22:48 10 Q. Okay. And a person of skill in the art -- well, and  
02:22:54 11 Sutent -- S-U-T-E-N-T, I think it is -- you've heard of  
02:22:58 12 that; correct?

02:22:58 13 A. Yes.

02:22:59 14 Q. That's a pharmaceutical product?

02:23:00 15 A. Yes.

02:23:01 16 Q. And it's a pharmaceutical product that's an example  
02:23:04 17 of a malic acid -- or being used in a formulation of  
02:23:10 18 crystalline malate salt; correct?

02:23:12 19 A. It's a malate salt. I think that's the way to say  
02:23:18 20 it.

02:23:18 21 Q. Okay. And that -- and it's used for treating cancer;  
02:23:21 22 is that right?

02:23:21 23 A. Yes.

02:23:22 24 Q. And it's right there on the label of the Sutent  
02:23:26 25 pharmaceutical product, that it's described as an (L)-malate

Trout - Cross

02:23:29 1 salt; correct?

02:23:30 2 A. Correct. And it's a different molecule than  
02:23:32 3 cabozantinib.

02:23:33 4 Q. Right. Exactly.

02:23:34 5 So -- and so, you talked a little bit about some  
02:23:44 6 lists -- some articles that listed potential counterions for  
02:23:51 7 use in making salts; correct?

02:23:52 8 A. Yes.

02:23:55 9 Q. And when -- just so for vocabular purposes, when we  
02:23:59 10 talk about counterions we're talking about something like  
02:24:02 11 malic acid; right?

02:24:03 12 A. Yeah. Ionized form, yes.

02:24:05 13 Q. And that's what will react with the base and  
02:24:07 14 hopefully make the salt, if that's what is going to happen;  
02:24:10 15 correct?

02:24:10 16 A. The nonionized form reacts with the base to hopefully  
02:24:16 17 make the ionized salt.

02:24:17 18 Q. Okay. And one of the -- you actually cited an  
02:24:24 19 article in your expert report concerning discussions of  
02:24:30 20 counterions that might be suitable for use; correct?

02:24:33 21 A. There were several articles cited. Yes.

02:24:37 22 Q. And -- yeah. And you took a chart -- a table out of  
02:24:40 23 one of those articles; correct?

02:24:42 24 A. You mean the Stahl article?

02:24:46 25 Q. Yes, exactly.



Trout - Cross

02:24:47 1 A. Yes.

02:24:47 2 Q. The Stahl article.

02:24:48 3 MR. LOMBARDI: So let's put the Stahl article up  
02:24:50 4 on the screen, PTX-610.

02:24:54 5 THE WITNESS: Again, please point me to the --  
02:24:54 6 BY MR. LOMBARDI:

02:24:55 7 Q. I'm sorry. Volume II, and look at the tabs. It  
02:25:00 8 will -- the tabs will tell you.

02:25:02 9 A. I got it. I got it. Thank you.

02:25:11 10 Oh, actually, I went to my report. You want to  
02:25:13 11 go to the article. Do you know the PTX?

02:25:23 12 Q. It's PTX-610.

02:25:30 13 A. Okay. I got it. Thank you.

02:25:32 14 Q. Okay. Tell me when you're there.

02:25:34 15 A. I'm there.

02:25:35 16 Q. Okay. And this is the Stahl article, S-T-A-H-L;  
02:25:40 17 correct?

02:25:41 18 A. Yes.

02:25:43 19 Q. And this is the one you cited in your report;  
02:25:46 20 correct?

02:25:46 21 A. I believe so. Yes.

02:25:53 22 MR. LOMBARDI: And Stahl, at Page 333 -- Exhibit  
02:26:04 23 Page 333.

02:26:04 24 BY MR. LOMBARDI:

02:26:04 25 Q. That's in the middle at the bottom, Doctor.

Trout - Cross

02:26:09 1 A. Okay.

02:26:13 2 Q. On that page, he refers to other reviews of  
02:26:17 3 pharmaceutical salts; correct?

02:26:19 4 A. The first sentence.

02:26:21 5 Q. Yes, exactly. That first sentence.

02:26:24 6 And he talks about comprehensive reviews on  
02:26:26 7 pharmaceutical salts by -- you say that Berge. Is that how  
02:26:30 8 you say it?

02:26:31 9 A. I think there's been some debate this week whether  
02:26:35 10 Berge or Berge.

02:26:36 11 Q. Whichever you want is fine with me.

02:26:38 12 A. French or German, I would say. Whatever.

02:26:40 13 Q. All right. Berge, Bighley and Monkhouse.

02:26:44 14 Do you see that?

02:26:44 15 A. Yes.

02:26:45 16 Q. And I think you said you've been here during trial  
02:26:51 17 and you saw the counsel for Exelixis discussed Bighley with  
02:26:57 18 Dr. Steed, I believe it was.

02:26:58 19 Do you remember that?

02:26:58 20 A. Yes.

02:27:00 21 Q. And you remember putting a chart up based on Bighley?

02:27:02 22 A. Yes.

02:27:03 23 Q. Okay. And if you go down to the third line in the  
02:27:08 24 middle. It says, "While these authors presented the results  
02:27:11 25 of a survey on the approval status of drug salts 25 years

Trout - Cross

02:27:16 1 ago, the present-day situation is different."

02:27:20 2 Do you see that?

02:27:21 3 A. Yes.

02:27:23 4 Q. "And accumulated knowledge and experience has led to  
02:27:26 5 a reduction of the number of acids and bases regarded as  
02:27:29 6 innocuous."

02:27:31 7 Do you see that?

02:27:32 8 A. Yes.

02:27:34 9 Q. "Therefore, it was" -- I'm skipping a line.

02:27:36 10 "Therefore, it was deemed timely to put up a  
02:27:39 11 revised list of useful salt-forming acids and bases."

02:27:44 12 Do you see that?

02:27:45 13 A. Yes.

02:27:46 14 Q. And is that one of the reasons you selected Stahl for  
02:27:49 15 your expert report, was its updated information?

02:27:53 16 A. I selected Stahl because of the table and what I  
02:27:57 17 discussed in my report.

02:27:58 18 Q. Okay. And it talks about -- in Stahl, it talks  
02:28:05 19 about -- well, let me strike the question.

02:28:07 20 A person of skill in the art would have been  
02:28:10 21 aware of something called Tong's Rule-of-2?

02:28:14 22 A. Yes. They've we've talked about that.

02:28:16 23 Q. Okay. And you talked about that.

02:28:18 24 It's a well-known rule of thumb; correct?

02:28:20 25 A. That's fair.

Trout - Cross

02:28:22 1 Q. And it was well-known in the early 2000s?

02:28:24 2 A. Yeah. Somewhere in the early 2000s, yeah.

02:28:31 3 Q. And a person of skill in the art would have been

02:28:33 4 aware of the Tong reference in that time frame; correct?

02:28:35 5 A. Yes.

02:28:38 6 Q. And a person of skill in the art would have been

02:28:42 7 motivated to select a counterion for salt screening with a

02:28:48 8  $pK_a$  at least two units lower than the base, based on Tong's

02:28:53 9 rule of thumb; correct?

02:28:56 10 A. No, Counsel. I can't agree with that. I think I've

02:28:58 11 talked about that extensively.

02:29:01 12 Q. Okay. Well, let me just make sure that we're talking

02:29:05 13 about the same thing here so that there's no confusion.

02:29:23 14 Do you agree that a person of skill in the art

02:29:26 15 would have been motivated to select counterions for

02:29:30 16 screening that had a  $pK_a$  of at least two pH units lower than

02:29:35 17 the compound being screened?

02:29:38 18 Do you agree with that?

02:29:39 19 A. I think that would be a consideration that would not

02:29:44 20 be -- it would not be exclusive as we've been talking about

02:29:47 21 today.

02:29:48 22 Q. Okay. Okay. And -- but it's something that a person

02:29:51 23 of skill in the art would consider in determining what acid

02:29:56 24 to choose in trying to make a salt; correct?

02:29:59 25 A. The skilled person would know it and taking it into

Trout - Cross

02:30:02 1 account, and it wouldn't be exclusive.

02:30:04 2 Q. Okay. And there were techniques at the time that a  
02:30:10 3 person of skill in the art would be able to undertake to  
02:30:13 4 determine  $pK_a$ ; right?

02:30:15 5 A. Yes.

02:30:17 6 Q. That was within the level of skill in the art at the  
02:30:19 7 time; is that right?

02:30:20 8 A. If the person wanted to, yes.

02:30:23 9 Q. And I think you've said you've heard in Court, but  
02:30:26 10 just so we say it, the  $pK_a$  for cabozantinib is 5.9, or  
02:30:32 11 around there at least?

02:30:33 12 A. That's the number Dr. Steed used. He never  
02:30:36 13 referenced that, but...

02:30:38 14 Q. Right. And the acceptable acids or counterions under  
02:30:43 15 the rule of thumb would have a  $pK_a$  of 3.9 or more; is that  
02:30:48 16 right?

02:30:48 17 A. Again, I think you mean less, but...

02:30:55 18 Q. I do.

02:30:56 19 A. Just trying to help you.

02:30:57 20 Q. Yeah, that's fine. That's fine. Do you want me to  
02:31:00 21 restate the question?

02:31:00 22 THE COURT: I think we've got it.

02:31:02 23 MR. LOMBARDI: Okay. That's fine.

02:31:03 24 BY MR. LOMBARDI:

02:31:03 25 Q. So -- so, a person could determine -- well, let me

Trout - Cross

02:31:10 1 just ask this: The Stahl chart also has a column that  
02:31:16 2 indicates G-R-A-S; correct?

02:31:19 3 A. Yes.

02:31:21 4 Q. Okay. And G-R-A-S stands for generally regarded as  
02:31:25 5 safe; correct?

02:31:26 6 A. Yeah, technically it's generally recognized as safe.  
02:31:30 7 I think that's what we've been talking about. I know it  
02:31:33 8 says "regarded" in the reference, but just to be clear.

02:31:36 9 Q. Okay. That's fine.

02:31:37 10 A. But that's close enough.

02:31:38 11 Q. And I'm not going to make you repeat this because  
02:31:41 12 you've done it already, but you've gone through in  
02:31:44 13 questioning at a deposition and determined kind of the  
02:31:47 14 overlap between G-R-A-S and Tong's Rule-of-2 for that chart  
02:31:54 15 in Stahl; is that right, with respect to cabozantinib?

02:31:56 16 A. I was asked GRAS --

02:32:03 17 Q. Yeah.

02:32:03 18 A. -- during my deposition; I do recall that.

02:32:05 19 Q. And when you find things that fit within the rule of  
02:32:07 20 thumb and things that are G-R-A-S from that chart, the Stahl  
02:32:12 21 chart, you come up with about nine acids; is that right?

02:32:16 22 Do you remember? If you don't remember...

02:32:18 23 A. I don't remember the exact number, as I testified in  
02:32:21 24 my deposition. That would not exclude the skilled person  
02:32:25 25 from incorporating others. So, it's not a really accurate

Trout - Redirect

02:32:28 1 number.

02:32:29 2 Q. Okay. Okay.

02:32:30 3 MR. LOMBARDI: No further questions, Your Honor.

02:32:31 4 THE COURT: All right. Any redirect?

02:32:33 5 MR. PRUSSIA: Briefly, Your Honor.

02:32:34 6 REDIRECT EXAMINATION

02:32:37 7 BY MR. PRUSSIA:

02:32:37 8 Q. So, Dr. Trout, you were asked some questions about  
02:32:40 9 paragraph 277 of your report in the first MSN case, do you  
02:32:43 10 recall that?

02:32:43 11 A. Yes.

02:32:44 12 Q. And the issue that you were addressing in that  
02:32:47 13 portion of your report was obviousness, do you remember  
02:32:51 14 that?

02:32:51 15 A. Yes.

02:32:52 16 Q. And in the MSN one litigation, Dr. Steed was offering  
02:32:56 17 the opinion that it was routine and predictable to arrive at  
02:33:00 18 form N-2; does that refresh your memory?

02:33:03 19 A. Yes.

02:33:03 20 Q. And in this litigation, MSN and Dr. Steed are arguing  
02:33:07 21 the direct opposite, that obtaining polymorphs would be  
02:33:10 22 unpredictable; right?

02:33:11 23 A. Yes.

02:33:13 24 Q. Now, for 103, which was the issue that you were  
02:33:16 25 discussing in your report, what's your understanding of

Trout - Redirect

02:33:20 1 whether the person of ordinary skill in the art would have  
02:33:23 2 had the benefit of the teachings of the specification of the  
02:33:28 3 crystalline malate salt patent?

02:33:29 4 A. The person would not have had the benefit of those  
02:33:31 5 teachings and even under 103.

02:33:34 6 Q. Thank you.

02:33:36 7 So in -- at the time you were making those  
02:33:38 8 statements, about what a person of ordinary skill in the art  
02:33:41 9 would have expected, was that with or without the benefit --  
02:33:45 10 with or without the benefit of the teachings of the  
02:33:48 11 specification of the crystallize malate salt patents?

02:33:50 12 A. That's without the benefit of those patents, the  
02:33:53 13 asserted patents here.

02:33:54 14 Q. And the issue that you're addressing in this case is  
02:33:56 15 you're responding to their arguments with respect to written  
02:33:59 16 description; right?

02:33:59 17 A. Correct.

02:34:01 18 Q. And what role does the specification play in  
02:34:04 19 determining whether the inventor has had possession of the  
02:34:07 20 invention under written description?

02:34:08 21 A. Well, as I explained in my direct, there's a whole  
02:34:12 22 host of detail in the specification, including experimental  
02:34:18 23 detail -- I think there are 27 figures -- a lot of data, a  
02:34:21 24 lot of information, including the text that we went over,  
02:34:24 25 which demonstrate that the inventors possessed crystalline



Trout - Redirect

02:34:28 1 cabozantinib malate.

02:34:30 2 Q. Now, with the guidance that's identified in the  
02:34:36 3 common specification, coupled with the knowledge of a person  
02:34:40 4 of ordinary skill in the art, would that have allowed a  
02:34:42 5 person of skill to perform a polymorph screen, and with a  
02:34:50 6 routine expectation of success, obtain and characterize  
02:34:53 7 additional polymorphs of crystalline cabozantinib  
02:34:56 8 (L)-malate?

02:34:56 9 A. If they were routine polymorphs from a routine  
02:34:59 10 screen, yes, they could have used the teaching to do that.

02:35:02 11 Q. And did MSN cite the crystalline malate salt patents  
02:35:06 12 in its patent application for form S?

02:35:08 13 A. Yes.

02:35:09 14 Q. And did Mylan and Cipla?

02:35:11 15 A. Yes.

02:35:12 16 Q. Now, you were asked some questions about form S. And  
02:35:15 17 just to make sure we're talking about the same thing,  
02:35:19 18 does -- what is the form of crystalline malate that's in the  
02:35:26 19 MSN ANDA product?

02:35:27 20 A. That's the MSN form S.

02:35:30 21 Q. And what form of crystalline cabozantinib malate is  
02:35:35 22 used in Cabometyx?

02:35:36 23 A. That's form N-2.

02:35:38 24 Q. And you understand that MSN has submitted an  
02:35:41 25 application to the FDA to market a generic version of

George - Direct

02:35:44 1 Cabometyx; do you understand that?

02:35:45 2 A. Yes.

02:35:46 3 Q. And has MSN represented to the FDA that its form S is  
02:35:51 4 bioequivalent to form N-2?

02:35:54 5 A. Yes.

02:35:55 6 MR. PRUSSIA: Nothing further.

02:35:57 7 THE COURT: All right. Dr. Trout, thank you.

02:35:59 8 You may step down. Watch your step.

02:36:01 9 THE WITNESS: Yes. Thank you.

02:36:08 10 MS. WIGMORE: Your Honor, Exelixis calls for its  
02:36:15 11 next witness Dr. Daniel George.

02:36:19 12 THE COURT: All right.

02:37:01 13 DEPUTY CLERK: Please state and spell your full  
02:37:02 14 name for the record.

02:37:02 15 THE WITNESS: Yes, it's Dr. Daniel James George.  
02:37:06 16 It's D-A-N-I-E-L J-A-M-E-S G-E-O-R-G-E.

02:37:16 17 DANIEL JAMES GEORGE, the witness herein, after  
02:37:16 18 having been duly sworn under oath, was examined and  
02:37:23 19 testified as follows:

02:37:23 20 THE WITNESS: I do.

02:37:25 21 MS. WIGMORE: May I proceed, Your Honor?

02:37:26 22 THE COURT: Yes.

02:37:27 23 DIRECT EXAMINATION

02:37:27 24 BY MS. WIGMORE:

02:37:27 25 Q. Good afternoon, Dr. George. Would you please

George - Direct

02:37:29 1 introduce yourself?

02:37:29 2 A. Hi, I'm Dr. Daniel George.

02:37:33 3 Q. Have you been retained by Exelixis, Inc., as an  
02:37:35 4 expert in this case?

02:37:36 5 A. I have.

02:37:38 6 Q. Generally speaking, what issues have you been asked  
02:37:40 7 to address?

02:37:41 8 A. I've been asked to address the clinical success  
02:37:44 9 associated with Cabometyx and the nexus between this  
02:37:47 10 clinical success and the patents in question.

02:37:50 11 MS. WIGMORE: Let's have PDX-7.2.

02:37:50 12 BY MS. WIGMORE:

02:37:53 13 Q. What is shown on this slide?

02:37:54 14 A. That's a picture of me and my -- summary of my  
02:37:57 15 education and experience.

02:37:58 16 Q. Where are you employed?

02:37:59 17 A. I am at Duke University.

02:38:01 18 Q. What do you do at Duke?

02:38:02 19 A. I'm a medical oncologist. I specialize in  
02:38:06 20 genitourinary cancers. So kidney, bladder, prostate cancer.  
02:38:10 21 And I also do research. I'm a professor of medicine.

02:38:12 22 Q. Have you been involved in any work involving tyrosine  
02:38:16 23 kinase inhibitors?

02:38:16 24 A. I have. Yes.

02:38:18 25 Q. Can you give us some examples?

George - Direct

02:38:19 1 A. Sure. Yeah, since my -- finishing my fellowship in  
02:38:23 2 1998. I was at Dana-Farber, did some early experiments with  
02:38:27 3 the early clinical trials with VEGF tyrosine kinase  
02:38:30 4 inhibitors. I moved to Duke and I've continued that work on  
02:38:33 5 up to the current day.

02:38:35 6 Q. For how long have you been researching tyrosine  
02:38:37 7 kinase inhibitors?

02:38:37 8 A. 25 years.

02:38:41 9 Q. Approximately what portion of your work involves  
02:38:43 10 treating patients?

02:38:43 11 A. About 40 percent.

02:38:46 12 Q. For how long have you been treating patients with  
02:38:49 13 kidney cancer?

02:38:49 14 A. For 25 years.

02:38:51 15 MS. WIGMORE: Let's please have PDX-7.3.

02:38:51 16 BY MS. WIGMORE:

02:38:54 17 Q. Dr. George, have you received any honors for your  
02:38:57 18 clinical work?

02:38:58 19 A. Yeah, overall, I mean, for my work at Duke, I was  
02:39:00 20 recently awarded Eleanor Easley Distinguished Chair in  
02:39:04 21 School of Medicine. I've also been recognized as a fellow  
02:39:07 22 of American Society of Clinical Oncology. In 2021, I was  
02:39:11 23 elected the chair of the Medical Steering Committee for the  
02:39:13 24 Kidney Cancer Association.

02:39:15 25 Q. What is the Kidney Cancer Association?

George - Direct

02:39:17 1 A. It's a non-profit advocacy group for patients with  
02:39:21 2 kidney cancer.

02:39:22 3 Q. If you could please turn to Tab 1 in your binder.

02:39:24 4 MS. WIGMORE: And pull up PTX-775.

02:39:24 5 BY MS. WIGMORE:

02:39:29 6 Q. What is this document?

02:39:31 7 A. That's my CV.

02:39:34 8 Q. Is this an accurate representation of your  
02:39:35 9 experience, publications, and honors and awards?

02:39:38 10 A. It is.

02:39:39 11 MS. WIGMORE: Your Honor, we offer Dr. Daniel  
02:39:41 12 George as an expert in the treatment of cancer, including  
02:39:45 13 renal cell carcinoma.

02:39:47 14 MR. COOPER: No objection.

02:39:48 15 THE COURT: You may proceed

02:39:50 16 BY MS. WIGMORE:

02:39:51 17 Q. Dr. George, are you familiar with the patent claims  
02:39:52 18 asserted in this case?

02:39:54 19 A. I am.

02:39:54 20 Q. Were you here when Dr. Trout testified the asserted  
02:39:57 21 claims of the crystalline malate salt patents cover  
02:40:00 22 Cabometyx?

02:40:01 23 A. Yes.

02:40:02 24 Q. And do you understand that Claim 3 of the low  
02:40:04 25 impurity patent covers Cabometyx?

George - Direct

02:40:06 1 A. Yes.

02:40:07 2 Q. Are you offering an ultimate opinion on the validity  
02:40:10 3 of any of the asserted claims?

02:40:12 4 A. Not an ultimate opinion.

02:40:14 5 MS. WIGMORE: Let's have PDX-7.4.

02:40:14 6 BY MS. WIGMORE:

02:40:17 7 Q. Could you briefly describe your opinions?

02:40:19 8 A. Yeah, I have three opinions: One that Cabometyx is  
02:40:23 9 and has been a clinical success in kidney cancer, that  
02:40:28 10 Cabometyx satisfies a long-felt unmet need in patients, and  
02:40:33 11 that there's a direct nexus between this clinical success  
02:40:37 12 and the asserted claims.

02:40:39 13 Q. And we'll come to those in detail momentarily.

02:40:42 14 MS. WIGMORE: But if we could please have  
02:40:44 15 PDX-7.5.

02:40:44 16 BY MS. WIGMORE:

02:40:45 17 Q. What information did you consider in forming your  
02:40:47 18 opinions?

02:40:47 19 A. I based this on a review of the literature as well as  
02:40:51 20 my extensive clinical experience as well as conversations  
02:40:55 21 with my colleagues, Dr. Trout and Dr. Myerson.

02:40:57 22 Q. Are you familiar with defendants' expert, Dr. Anthony  
02:41:01 23 Mega?

02:41:02 24 A. I am.

02:41:02 25 Q. Have you reviewed the opinions he has offered in this

George - Direct

02:41:05 1 case?

02:41:05 2 A. Yes, I have.

02:41:07 3 Q. Are you prepared to respond to those today?

02:41:08 4 A. Yes.

02:41:10 5 MS. WIGMORE: Let's have PDX-7.6.

02:41:10 6 BY MS. WIGMORE:

02:41:13 7 Q. What is Cabometyx?

02:41:13 8 A. This is Cabometyx. It's a product that we prescribe  
02:41:18 9 regularly in clinic to patients with advanced kidney cancer.  
02:41:22 10 And shown here in three formulations, 60 milligrams,  
02:41:26 11 40 milligrams and 20 milligrams.

02:41:27 12 Q. Are you familiar with Cometriq?

02:41:29 13 A. I am. Yes.

02:41:30 14 Q. And what is Cometriq?

02:41:31 15 A. Cometriq is a capsule form of cabozantinib similar to  
02:41:36 16 Cabometyx, and it's prescribed for the treatment of  
02:41:39 17 medullary thyroid cancer.

02:41:41 18 Q. What is the active ingredient in Cabometyx and  
02:41:43 19 Cometriq?

02:41:43 20 A. It's crystalline Cabometyx (L)-malate.

02:41:47 21 Q. And is that cabozantinib?

02:41:49 22 A. Sorry. Yes. Crystalline cabozantinib (L)-malate.

02:41:52 23 Q. Now, for the purpose of your testimony today, will  
02:41:54 24 you focus on Cabometyx?

02:41:56 25 A. I will, yes.

George - Direct

02:41:57 1 Q. When was Cabometyx first approved by the Food & Drug  
02:42:01 2 Administration?

02:42:01 3 A. In 2016.

02:42:04 4 Q. Please turn to Tab 2 in your binder, which is PTX-1.  
02:42:08 5 What is this document?

02:42:11 6 A. This is a patent for the -- for cabozantinib.

02:42:22 7 Q. I think you might be at the wrong tab. We're looking  
02:42:24 8 at PTX-1.

02:42:25 9 A. Oh, sorry. Oh, 1. Sorry.

02:42:28 10 Q. What is PTX --

02:42:29 11 A. Oh, yeah, yeah. Sorry, it's up on the screen. This  
02:42:31 12 is the prescribing information for Cabometyx.

02:42:35 13 Q. Is this sometimes referred to as the label or the  
02:42:37 14 package insert?

02:42:38 15 A. That's right.

02:42:39 16 Q. Now, if you could focus on the section in the  
02:42:42 17 left-hand side of the first page titled "Indications and  
02:42:45 18 Usage."

02:42:46 19 Do you see that?

02:42:47 20 A. I do. Yes.

02:42:48 21 Q. Are you familiar with the approved indications for  
02:42:51 22 Cabometyx?

02:42:51 23 A. I am. Yes.

02:42:53 24 Q. What indications are you focusing on in your  
02:42:55 25 testimony here today?



George - Direct

02:42:56 1 A. The first two, where one is for advanced renal cell  
02:43:02 2 carcinoma.

02:43:02 3 Q. And what are those specific indications.

02:43:05 4 A. The first is for patients with advanced renal cell  
02:43:08 5 carcinoma, and the second is for patients with advanced  
02:43:09 6 renal cell carcinoma as a first-line treatment in  
02:43:12 7 combination with nivolumab.

02:43:15 8 Q. What is renal cell carcinoma or RCC?

02:43:17 9 A. Renal cell carcinoma refers to the most common form  
02:43:20 10 of kidney cancer. It's over 90 percent of kidney cancers  
02:43:24 11 and its tumors are cancers that originate out of the kidney.

02:43:27 12 Q. What is first-line treatment?

02:43:28 13 A. First-line treatment refers to treatment that we give  
02:43:32 14 to patients who have not received any prior systemic therapy  
02:43:35 15 for advanced renal cell carcinoma.

02:43:37 16 Q. What is subsequent line treatment?

02:43:39 17 A. So subsequent line treatment refers to any treatment  
02:43:42 18 that patients received after receiving a first-line  
02:43:45 19 treatment.

02:43:45 20 Q. What is nivolumab?

02:43:47 21 A. Nivolumab is an immunotherapy. It's an antibody  
02:43:51 22 targeted against a protein PD-1. It's also referred to as  
02:43:55 23 an immuno checkpoint inhibitor.

02:43:57 24 Q. Now, we'll focus on kidney cancer today, but  
02:44:00 25 generally speaking is Cabometyx approved for any other

George - Direct

02:44:03 1 cancers?

02:44:03 2 A. It's also approved, yes, for hepatocellular carcinoma  
02:44:08 3 and differentiated thyroid cancer.

02:44:11 4 Q. Are you familiar with a concept of breakthrough  
02:44:14 5 therapy designation?

02:44:14 6 A. I am, yes.

02:44:15 7 Q. What is that?

02:44:16 8 A. That's an FDA distinction for new drugs undergoing  
02:44:21 9 review for indication. It's regulatory approval --  
02:44:26 10 regulatory process to accelerate the approval process. And  
02:44:29 11 it's granted at the request of the -- of the sponsor.

02:44:33 12 Q. How, if at all, does breakthrough therapy designation  
02:44:36 13 apply to Cabometyx?

02:44:38 14 A. Cabometyx received breakthrough designation when it  
02:44:42 15 was under review for the first indication of advanced renal  
02:44:46 16 cell carcinoma.

02:44:46 17 Q. Did Cabometyx receive that designation for any other  
02:44:49 18 indication?

02:44:49 19 A. Yes. Also when it was under review for  
02:44:54 20 differentiated thyroid cancer.

02:44:56 21 MS. WIGMORE: If we could turn to Tab 3 in your  
02:44:58 22 binder which is PTX-528. I'd like to move to your first  
02:45:03 23 opinion regarding clinical success.

02:45:03 24 BY MS. WIGMORE:

02:45:06 25 Q. What is PTX-528?

George - Direct

02:45:08 1 A. This is the NCCN, or *National Comprehensive Cancer*  
02:45:12 2 *Network Practice Guidelines for Kidney Cancer*.

02:45:15 3 Q. What is the date of the document?

02:45:16 4 A. June 21, 2023.

02:45:19 5 Q. How is this document used by clinicians?

02:45:22 6 A. You know, this is helpful for clinicians in two ways.  
02:45:24 7 One, it really helps guide our practice. It gives us a -- a  
02:45:28 8 reference in which to justify or back up the treatments that  
02:45:33 9 we choose for our patients. It also helps with approval  
02:45:36 10 process with -- with papers.

02:45:39 11 MS. WIGMORE: If we could please turn to Page 15  
02:45:41 12 that ends in Bates Number 1680.

02:45:41 13 BY MS. WIGMORE:

02:45:45 14 Q. What is clear cell histology?

02:45:48 15 A. Yeah. Clear cell histology refers to the most common  
02:45:54 16 form of renal cell carcinoma. It's about 75, 80 percent of  
02:45:59 17 renal cell carcinomas.

02:46:01 18 Q. Generally speaking, what does this table on Page 15  
02:46:04 19 of the NCCN Guidelines address?

02:46:07 20 A. So, this table is sort of a summary, if you will, of  
02:46:11 21 the recommendations from the panel. You'll see on the far  
02:46:14 22 left, risk categories. This refers to the prognostic status  
02:46:19 23 of patients. Favorable risk is obviously better than the  
02:46:22 24 patients who have poor or intermediate risk features, and  
02:46:25 25 then next to that is a column for preferred regimens. These

George - Direct

02:46:28 1 are the recommendations from the panel consensus  
02:46:32 2 recommendations.

02:46:32 3 Q. Now, how does this table address Cabometyx  
02:46:38 4 specifically?

02:46:38 5 A. Yeah, Cabometyx is in several of these  
02:46:41 6 recommendations. You'll see for favorable risk preferred  
02:46:43 7 regimens, cabozantinib or Cabometyx is listed in combination  
02:46:48 8 with nivolumab. It's a Category I recommendation, which is  
02:46:51 9 the highest recommendation. And then you'll see it listed  
02:46:55 10 twice in the poor and intermediate risk categories, once  
02:46:58 11 again, with -- in combination with nivolumab is Category I.  
02:47:02 12 And then it's the only VEGF tyrosine kinase inhibitor listed  
02:47:07 13 as a single agent in this category by itself as monotherapy.

02:47:13 14 Q. Now, you've referred to this combination of Cabometyx  
02:47:16 15 and nivolumab.

02:47:17 16 A. Yes.

02:47:17 17 Q. How, if at all, does Cabometyx contribute to the  
02:47:20 18 success of that combination?

02:47:22 19 A. Yeah, that combination is the most recent clinical  
02:47:25 20 data around cabozantinib and nivolumab in the front-line  
02:47:30 21 setting, and it demonstrated a significant improvement in  
02:47:35 22 the delay to disease progression in overall survival for  
02:47:39 23 patients. In that study, the results of that combination  
02:47:43 24 outperformed what either cabozantinib alone or what  
02:47:47 25 nivolumab alone had been able to show. So it was really the

George - Direct

02:47:51 1 combination of both drugs working together to produce those  
02:47:53 2 results.

02:47:54 3 Q. Now, you pointed out that that table refers to  
02:47:57 4 cabozantinib. Is there any other form of cabozantinib  
02:48:01 5 approved to treat kidney cancer besides Cabometyx?

02:48:04 6 A. No, there is not.

02:48:06 7 Q. Could you please explain how Cabometyx has impacted  
02:48:09 8 your patients?

02:48:10 9 A. Yeah. You know, for our patients since 2016, when  
02:48:14 10 this first became available, Cabometyx really changed the  
02:48:18 11 landscape for our patients. This created a treatment option  
02:48:20 12 for the first time that extended survival for patients for  
02:48:23 13 the majority of patients in the subsequent lines of therapy.  
02:48:28 14 And it was really a life extending therapy for patients. It  
02:48:31 15 gave them hope.

02:48:32 16 Since then we've been able to use this drug now  
02:48:35 17 in the first-line setting where we're seeing extended  
02:48:37 18 disease periods of control near complete responses in  
02:48:41 19 patients. I have patients now on this drug literally for  
02:48:45 20 years. It's changed the life of patients with kidney  
02:48:48 21 cancer.

02:48:48 22 Q. If you could please turn to Tab 4 in your binder  
02:48:52 23 which is PTX-363.

02:48:54 24 What is this document?

02:48:55 25 A. This is the *Lancet Oncology* publication for the

George - Direct

02:49:00 1 METEOR study. This was the pivotal trial that led to the  
02:49:03 2 first FDA indication for Cabometyx.

02:49:07 3 Q. And what was compared in this study?

02:49:09 4 A. So this is a Phase 4 study comparing cabozantinib  
02:49:12 5 versus everolimus in patients with advanced renal cell  
02:49:16 6 carcinoma treated with one or more prior VEGF tyrosine  
02:49:20 7 kinase inhibitors.

02:49:20 8 Q. If you could turn, please, to the section titled  
02:49:23 9 "Interpretation" toward the bottom of the first page.

02:49:26 10 A. Yes.

02:49:27 11 Q. Please read the first two sentences in that  
02:49:29 12 paragraph.

02:49:29 13 A. "Treatment with cabozantinib increased overall  
02:49:32 14 survival, delayed disease progression, and improved the  
02:49:36 15 objective response compared with everolimus. Based on these  
02:49:40 16 results, cabozantinib should be considered a new standard of  
02:49:44 17 care treatment option for patients previously -- previously  
02:49:47 18 treated patients with advanced renal cell carcinoma."

02:49:50 19 Q. If you could turn, please, to Tab 5 in your binder,  
02:49:53 20 which is PTX-366.

02:49:56 21 What is this document?

02:49:56 22 A. This is the *Journal of Clinical Oncology*, or JCO,  
02:50:01 23 publication for the CABOSUN study, a comparison of  
02:50:05 24 cabozantinib versus sunitinib as initial therapy for  
02:50:08 25 patients with advanced renal cell carcinoma.

George - Direct

02:50:11 1 Q. What is sunitinib?

02:50:12 2 A. Sunitinib has otherwise been referred to as Sutent.

02:50:15 3 This is another spectrum selective VEGF tyrosine kinase

02:50:19 4 inhibitor that was really the standard of care in the

02:50:23 5 first-line treatment of patients with advanced renal cell

02:50:26 6 carcinoma at the time.

02:50:26 7 Q. Could you please turn to the conclusion section on

02:50:29 8 the first page of this document, and read the conclusion for

02:50:33 9 the record?

02:50:34 10 A. "Cabozantinib demonstrated a significant clinical

02:50:37 11 benefit in the progression free survival in overall response

02:50:42 12 rate over standard of care sunitinib as first-line therapy

02:50:46 13 in patients with intermediate or poor risk metastatic renal

02:50:50 14 cell carcinoma."

02:50:50 15 Q. Let's turn to Tab 6 in your binder, which is PTX-367.

02:50:55 16 What is this document?

02:50:55 17 A. This is the *New England Journal of Medicine*

02:51:00 18 publication for the CheckMate 9ER study. This was a Phase 3

02:51:03 19 study comparing the combination of nivolumab plus

02:51:07 20 cabozantinib versus sunitinib for patients with advanced

02:51:09 21 renal cell carcinoma.

02:51:11 22 Q. Could you please turn to the conclusions section?

02:51:14 23 A. Yes.

02:51:14 24 Q. And what does the first sentence of the conclusion of

02:51:18 25 the study show?

George - Direct

02:51:19 1 A. Nivolumab plus cabozantinib had significant benefits  
02:51:23 2 over sunitinib with respect to progression free survival,  
02:51:27 3 overall survival and likelihood of response in patients with  
02:51:31 4 previously untreated advanced renal cell carcinoma.

02:51:34 5 MS. WIGMORE: Let's turn to Tab 7 in your  
02:51:36 6 binder, which is PTX-470.

02:51:39 7 THE WITNESS: Yes.

02:51:39 8 BY MS. WIGMORE:

02:51:39 9 Q. What is this document?

02:51:40 10 A. This is the Contact-03 publication from this year in  
02:51:45 11 the journal *Lancet*, and it was a comparison -- a Phase 3  
02:51:49 12 study comparing the combination of atezolizumab plus  
02:51:53 13 cabozantinib versus cabozantinib monotherapy for patients  
02:51:57 14 with renal cell carcinoma after progression with previous  
02:52:00 15 immune checkpoint inhibitor.

02:52:02 16 Q. What is atezolizumab?

02:52:04 17 A. Atezolizumab is another immune checkpoint. It's  
02:52:10 18 monoclonal antibody targeting the PD-L1 protein, which is  
02:52:12 19 the protein that activates the PD1 receptor, so similar  
02:52:17 20 pathway.

02:52:17 21 Q. Similar pathway to?

02:52:19 22 A. To nivolumab sulfate.

02:52:21 23 MS. WIGMORE: If you could turn to the findings.

02:52:21 24 BY MS. WIGMORE:

02:52:23 25 Q. And I want to direct your attention to the sentence



George - Direct

02:52:25 1 beginning "median."

02:52:28 2 Do you see that?

02:52:28 3 A. I do. Yes.

02:52:29 4 Q. What does that sentence convey about cabozantinib

02:52:35 5 versus the combination of cabozantinib and atezolizumab?

02:52:38 6 A. Yeah. So the top level results from the study  
02:52:41 7 demonstrated that the median progression free survival for  
02:52:44 8 the combination with atezolizumab and cabozantinib was  
02:52:47 9 10.6 months, but for cabozantinib monotherapy it was  
02:52:51 10 10.8 months. Essentially, overlapping results in terms of  
02:52:56 11 the effectiveness of these two arms, but with greater side  
02:53:00 12 effects associated with the combination.

02:53:02 13 Q. Does that mean that this was a failed study?

02:53:04 14 A. Not at all. I mean, clinical trials are designed to  
02:53:07 15 answer a question and the question here was: Is there value  
02:53:10 16 to continuing with an immune checkpoint inhibitor in this  
02:53:14 17 subsequent line of therapy, and this definitively answered  
02:53:17 18 the question, just the answer is no, that cabozantinib  
02:53:20 19 monotherapy was really as effective as any other -- as the  
02:53:26 20 combination would be in this setting.

02:53:27 21 Q. What, if anything, did this study reveal about  
02:53:29 22 treatment with cabozantinib alone?

02:53:31 23 A. Well, you know, this is the new landscape of renal  
02:53:35 24 cell carcinoma. When the METEOR study was done, there were  
02:53:37 25 very few immune checkpoint inhibitor patients treated, so

George - Direct

02:53:41 1 now we're in a new situation where immune therapies are  
02:53:44 2 really the standard of care. This really provides a context  
02:53:47 3 for what we can expect for patients receiving Cabometyx now  
02:53:52 4 in this subsequent line therapy. And the results were  
02:53:55 5 actually better than what we saw with METEOR. If anything,  
02:53:58 6 this agent is even more relevant than it was seven years  
02:54:01 7 ago.

02:54:02 8 Q. Dr. George, from your perspective as a clinician, has  
02:54:06 9 Cabometyx been clinically successful?

02:54:08 10 A. Absolutely.

02:54:10 11 Q. How does that clinical success bear on your decision  
02:54:12 12 to prescribe Cabometyx?

02:54:14 13 A. Yeah. I prescribe Cabometyx routinely for my  
02:54:18 14 patients, either in the first line or in the subsequent line  
02:54:21 15 therapy, over 90 percent of my patients are receiving  
02:54:23 16 Cabometyx at some point in their journey.

02:54:27 17 Q. Would an oncologist continue to prescribe a drug that  
02:54:30 18 does not work?

02:54:30 19 A. No. Oncologists base their decisions on both the  
02:54:35 20 literature that we've just reviewed, as well as their own  
02:54:37 21 clinical experience. If a drug is not performing in their  
02:54:41 22 experience with patients, if they're not tolerating it or if  
02:54:44 23 the drug is not demonstrating clinical benefit, they're  
02:54:46 24 going to stop using it.

02:54:47 25 MS. WIGMORE: Let's turn to PDX-7.7.

George - Direct

02:54:47 1 BY MS. WIGMORE:

02:54:50 2 Q. Now, what is the second opinion you're offering in  
02:54:53 3 this case?

02:54:53 4 A. That Cabometyx satisfied a long felt, unmet clinical  
02:54:58 5 need.

02:55:00 6 Q. As of 2011, was there a need for improved kidney  
02:55:04 7 cancer therapies?

02:55:05 8 A. Absolutely.

02:55:06 9 Q. Was the same true as of 2009?

02:55:08 10 A. Yes.

02:55:10 11 Q. How, if at all, did Cabometyx address that need?

02:55:12 12 A. Well, you know, at the time we had really kind of a  
02:55:15 13 handful of these VEGF targeted TKIs or mTOR inhibitors, like  
02:55:21 14 everolimus. But the truth was if you look at our Medicare  
02:55:24 15 data from that time, median survivals were about a year.  
02:55:27 16 Our best patients, from clinical trial data, the median  
02:55:30 17 survivals were a little over two years. This isn't long  
02:55:33 18 enough. And these patients were all progressing on these  
02:55:36 19 first line therapies within a year or so. They needed other  
02:55:39 20 therapy.

02:55:39 21 Everolimus, at the time, was the only approved  
02:55:42 22 therapy and it was based on modest delay of progression of  
02:55:46 23 disease with no survival benefit. Cabometyx met that need.  
02:55:49 24 It demonstrated greater survival, greater disease -- delay  
02:55:54 25 in disease progression, and response.

George - Direct

02:55:57 1 Q. To the extent Dr. Mega suggests that Cabometyx  
02:56:00 2 offered only a difference of degree in comparison to  
02:56:05 3 existing therapies, do you agree?

02:56:06 4 A. No. I don't.

02:56:07 5 Q. What are the reasons you do not agree?

02:56:09 6 A. Well, first off, this is a different drug. Now, I  
02:56:12 7 know all the VEGF inhibitor TKIs vary, but this is the only  
02:56:16 8 one that was intentionally selected to be both a MET  
02:56:20 9 inhibitor and a VEGF inhibitor. And the reason for that was  
02:56:23 10 the biology of MET, which we went over in the last trial,  
02:56:26 11 and the reason why that was important in kidney cancer,  
02:56:29 12 particularly kidney cancer that was resistant, where did  
02:56:32 13 this study show the benefit first? In exactly that patient  
02:56:35 14 population.

02:56:35 15 And then we studied it in the other population,  
02:56:38 16 the patients with the intermediate and poor risk patients  
02:56:41 17 that were rapidly progressing on sunitinib in the front line  
02:56:45 18 setting, and we demonstrated a superiority there that no  
02:56:47 19 other VEGF tyrosine kinase inhibitor had been able to show  
02:56:51 20 superiority versus sunitinib, even though others had tried.

02:56:55 21 So the clinical data really spoke to this drug  
02:56:58 22 demonstrating unmet needs and also benefits that no other  
02:57:02 23 VEGF TKI had shown.

02:57:04 24 Q. Is there a need for additional kidney cancer  
02:57:06 25 therapies today?

George - Direct

02:57:07 1 A. Absolutely.

02:57:09 2 Q. Does that change your opinion about whether Cabometyx  
02:57:12 3 fulfilled a long felt, unmet need?

02:57:14 4 A. Absolutely not.

02:57:15 5 Q. Why not?

02:57:16 6 A. Well, the truth is that our patients are still dying  
02:57:20 7 today and the death rate associated with kidney cancer  
02:57:23 8 hasn't gone down. We've delayed that time, but -- and  
02:57:26 9 people are living longer than ever, but they're still dying  
02:57:29 10 from this disease.

02:57:30 11 What Cabometyx has done is it's changed the  
02:57:32 12 landscape, it's allowed patients to live longer and that  
02:57:36 13 matters. Anybody that's known somebody who has died from  
02:57:39 14 metastatic cancer, whether it's kidney cancer or any cancer,  
02:57:42 15 knows that prolonging survival matters and it doesn't matter  
02:57:46 16 if it's a few months or a year. That time matters.

02:57:49 17 So having drugs that can do that, that can be a  
02:57:51 18 bridge to another therapy, it's hope. It's what our  
02:57:55 19 patients are really after.

02:57:56 20 MS. WIGMORE: Let's go to PDX-7.8.

02:57:56 21 BY MS. WIGMORE:

02:58:00 22 Q. Have you considered whether there's a nexus between  
02:58:02 23 the asserted claims in this case and the clinical benefits  
02:58:06 24 of Cabometyx?

02:58:06 25 A. I have.

George - Direct

02:58:07 1 Q. What is your opinion?

02:58:08 2 A. Well, Cabometyx is what has worked in our clinic.  
02:58:12 3 Cabometyx is what I prescribe. It's what our patients are  
02:58:15 4 taking and they're taking it in the context -- not of a  
02:58:18 5 clinical trial or controlled environment, but in real life  
02:58:21 6 and they're dealing with it with the medications and the  
02:58:26 7 concomitant drugs they have to take with the delays in  
02:58:28 8 discontinuations they have to go through for other medical  
02:58:31 9 issues and the travel or whatever circumstances they're  
02:58:34 10 living in. The drug is stable. The drug is effective. The  
02:58:37 11 drug is safe. The fact that we don't have this risk of --  
02:58:44 12 you know, of genotoxic impurities. All of this matters for  
02:58:50 13 our patients.

02:58:51 14 Q. You mentioned genotoxic impurities. Just briefly  
02:58:53 15 remind us what that is.

02:58:54 16 A. Yeah. So that refers to chemical degraded products  
02:58:59 17 from -- from the compound, in this case Cabometyx, that  
02:59:02 18 could be harmful, particularly damaging to DNA.

02:59:05 19 Q. Are genotoxins the same as side effects?

02:59:08 20 A. No. Side effects refer to complications that  
02:59:11 21 patients experience from the active pharmaceutical  
02:59:15 22 ingredient, in this case Cabometyx. And typically from  
02:59:19 23 effects that are on targets, meaning when we block this VEGF  
02:59:23 24 receptor, we're having effects not just on the cancer but in  
02:59:26 25 the whole body. That's why when we block that -- it

George - Direct

02:59:28 1 tightens the blood vessels, it's why we get diarrhea or high  
02:59:31 2 blood pressure because we're blocking water absorption and  
02:59:34 3 things like that.

02:59:35 4 Q. And is genotoxic -- a genotoxic side effect different  
02:59:39 5 from that?

02:59:39 6 A. Yeah. So genotoxic side effects are silent, patients  
02:59:42 7 don't feel them. Like they can't tell if something like  
02:59:45 8 that is going on, but it could be going in insidiously in  
02:59:48 9 their body and in their cells, and it has the risk over time  
02:59:51 10 of ultimately causing cancer.

02:59:53 11 Q. Have genotoxic impurities presented challenges for  
02:59:57 12 any other drug products?

02:59:58 13 A. Yeah, they have.

02:59:59 14 Q. Can you give us an example?

03:00:01 15 A. Yeah. One that I'm aware of is this drug valsartan  
03:00:05 16 or Diovan. It was an antihypertensive drug that we used in  
03:00:08 17 clinic and it got pulled because it was associated with --  
03:00:11 18 it was found to have genotoxic impurities that were  
03:00:14 19 increasing the risk of cancer.

03:00:16 20 Q. Now what, if any, role does the formulation of  
03:00:19 21 Claim 3 of the '349 patent play in the clinical success of  
03:00:23 22 Cabometyx?

03:00:24 23 A. Well, when I treat patients with Cabometyx,  
03:00:27 24 I don't -- I don't worry about, you know, what form this is.  
03:00:31 25 I know this is coming from -- you know, from Exelixis. I

George - Direct

03:00:36 1 know what this is. This is the crystalline form of  
03:00:40 2 cabozantinib (L)-malate and that gives me confidence. I  
03:00:43 3 know what I'm prescribing to these patients and I know that  
03:00:46 4 it's safe.

03:00:47 5 I know it has side effects and not everyone is  
03:00:49 6 going to tolerate it, but I can manage those things. It's  
03:00:52 7 the things that we don't know, the things that we can't  
03:00:54 8 measure that worry us, particularly now that we're using a  
03:00:57 9 drug in a setting where patients are living potentially for  
03:01:00 10 years on this drug.

03:01:01 11 Q. Now, in the previous trial against MSN concerning the  
03:01:06 12 '473 patent, you testified that the cabozantinib compound  
03:01:08 13 contributed to the success of Cabometyx.

03:01:10 14 Do you recall that?

03:01:11 15 A. I do.

03:01:13 16 Q. Does the fact that the cabozantinib compound impacts  
03:01:16 17 clinical success mean -- mean that the other features of  
03:01:19 18 Cabometyx do not?

03:01:20 19 A. Not at all.

03:01:21 20 Q. Why not?

03:01:22 21 A. Well, you know, cabozantinib (L)-malate in the  
03:01:27 22 crystalline form, I mean that's -- that's the whole  
03:01:29 23 molecule. What we study in the laboratory, what was  
03:01:31 24 designed and originally selected for, that -- that's not the  
03:01:35 25 drug product that we're ultimately treating patients with.



George - Cross

03:01:38 1 It's Cabometyx. It's the whole combination that ultimately  
03:01:42 2 is playing out in our patients and that's important.

03:01:44 3 I can't distill down the pieces of this and put  
03:01:48 4 percentages on what -- you know, how much -- what each is  
03:01:51 5 working. I just need to know that what I'm prescribing for  
03:01:54 6 patients is associated with the clinical data that we've  
03:01:58 7 studied and that I'm seeing play out on my patients  
03:02:01 8 individually.

03:02:03 9 MS. WIGMORE: Thank you, Dr. George. I have no  
03:02:05 10 further questions.

03:02:05 11 I would move to admit PTX-775, PTX-528, PTX-363,  
03:02:13 12 PTX-366, PTX-367 and PTX-470.

03:02:19 13 MR. COOPER: No objection.

03:02:21 14 THE COURT: Admitted without objection.

03:02:23 15 (PTX Exhibit Nos. 363, 366, 367, 470, 528, and  
03:02:08 16 775, were admitted into evidence.)

03:03:07 17 MR. COOPER: May I proceed?

03:03:07 18 THE COURT: Yeah.

03:02:24 19 CROSS-EXAMINATION

03:02:29 20 BY MR. COOPER:

03:03:08 21 Q. Good afternoon, Dr. George. Good to see you again?

03:03:10 22 A. Good to see you, too.

03:03:11 23 Q. Now, Doctor George, in forming your opinions for this  
03:03:14 24 case, you believed that any drug that extends the lives of  
03:03:18 25 patients beyond previously available therapies is meeting a

George - Cross

03:03:23 1 long felt, unmet need; correct?

03:03:25 2 A. Yes.

03:03:26 3 Q. And of course you'd agree that there were drugs  
03:03:29 4 available that were approved before Cabometyx that extended  
03:03:34 5 the lives of patients beyond the available RCC treatments  
03:03:39 6 that were then available; correct?

03:03:40 7 A. Actually that's not true.

03:03:43 8 Q. Well, let me ask you this: After Cabometyx was  
03:03:45 9 approved, there have been about six new regimens that have  
03:03:48 10 extended the lives of RCC patients beyond previously  
03:03:52 11 available therapies; correct?

03:03:53 12 A. That's true.

03:03:54 13 Q. And there is still an unmet need today to improve RCC  
03:03:59 14 treatment on both the front line and subsequent line  
03:04:03 15 treatments for RCC; correct?

03:04:04 16 A. Yes.

03:04:05 17 Q. All right. Let's go back to 2009.

03:04:07 18 By 2009, there were eight TKIs that had been  
03:04:12 19 approved for cancer treatment other than cabozantinib;  
03:04:16 20 correct?

03:04:16 21 A. Yes.

03:04:17 22 Q. Those are imatinib; yes?

03:04:19 23 A. I'm sorry?

03:04:19 24 Q. Imatinib?

03:04:21 25 A. No, imatinib wasn't approved in renal cell carcinoma.

George - Cross

03:04:24 1 Q. That was -- my question was for cancer?

03:04:26 2 A. Oh, for cancer, yes, absolutely. Sorry.

03:04:28 3 Q. Gefitinib; right?

03:04:29 4 A. Yes.

03:04:30 5 Q. Erlotinib?

03:04:31 6 A. Yes.

03:04:32 7 Q. Sorafenib?

03:04:33 8 A. Yes.

03:04:33 9 Q. Sunitinib?

03:04:34 10 A. Yes.

03:04:35 11 Q. Dasatinib?

03:04:36 12 A. Yes.

03:04:36 13 Q. Nilotinib?

03:04:37 14 A. Yes.

03:04:37 15 Q. Pazopanib; correct?

03:04:40 16 A. Yes.

03:04:41 17 Q. And as a group by 2009, these TKIs had demonstrated

03:04:47 18 clinical efficacy or benefits in several tumor types,

03:04:51 19 including kidney cancer, lung cancer, breast cancer, and

03:04:55 20 chronic leukemia; correct?

03:04:57 21 A. Yes.

03:04:57 22 Q. And each of those eight TKIs I just mentioned, except

03:05:04 23 Gefitinib and erlotinib are known to be spectrum selective;

03:05:09 24 correct?

03:05:09 25 A. That's correct.

George - Cross

03:05:11 1 Q. And the term "spectrum selective," that refers to a  
03:05:14 2 drug that simultaneously inhibits multiple kinases that are  
03:05:19 3 implicated in various forms of cancer; correct?

03:05:21 4 A. That's correct.

03:05:23 5 Q. And then there are also TKIs that were approved after  
03:05:28 6 2009 to treat various forms of cancer that are spectrum  
03:05:32 7 selective as well; correct?

03:05:34 8 A. That's right.

03:05:34 9 Q. And a few of those are vandetanib, lenvatinib, and  
03:05:39 10 axitinib are just a few; correct?

03:05:41 11 A. Yes.

03:05:41 12 Q. And each of the spectrum-selective TKI drugs has its  
03:05:47 13 own unique inhibition profile when it comes to their TKI  
03:05:52 14 targets; correct?

03:05:53 15 Except for erlotinib and Gefitinib, of the ones  
03:05:57 16 that I've -- we just talked about; is that true?

03:05:59 17 A. Yeah, that's generally true, yes.

03:06:01 18 Q. And even though none of them have the exact same TKI  
03:06:05 19 targets, other TKIs have some overlapping targets with  
03:06:10 20 cabozantinib; true?

03:06:11 21 A. Yeah. None of the ones you mentioned block MET.

03:06:16 22 Q. Right. But there are other overlapping TKI targets  
03:06:19 23 that the -- that some of the other TKIs have with  
03:06:23 24 cabozantinib; correct?

03:06:24 25 A. That's true.

George - Cross

03:06:26 1 Q. Now, one of the TKI targets you mentioned that  
03:06:29 2 Cabometyx inhibits is VEGFR; right?

03:06:32 3 A. Yes.

03:06:33 4 Q. And both in 2009 and at the time later at Cabometyx's  
03:06:38 5 approval, anti-VEGFR treatment was the standard of care for  
03:06:43 6 RCC therapy; correct?

03:06:44 7 A. That's right.

03:06:46 8 Q. And -- but sunitinib, sorafenib, and pazopanib, those  
03:06:50 9 were the first three anti-VEGFR TKIs to be approved for  
03:06:55 10 front line RCC treatment; right?

03:06:58 11 A. Yes. Sorafenib, actually, after cytokine therapy,  
03:07:02 12 but the other two, yes.

03:07:04 13 Q. And cabozantinib entered the market after those VEGFR  
03:07:07 14 inhibitors; correct?

03:07:08 15 A. That's right.

03:07:09 16 Q. Cabometyx received an indication for RCC first-line  
03:07:13 17 therapy in 2017; true?

03:07:15 18 A. In 20 -- the first-line treatment --

03:07:18 19 Q. First line?

03:07:19 20 A. -- on the -- I think it was 2019.

03:07:21 21 Q. Oh, okay. Thank you.

03:07:22 22 So, let's -- looking at about the 2015 to 2017  
03:07:27 23 time frame, before and after Cabometyx was first initially  
03:07:30 24 approved at all, you prescribed sunitinib to about 40 to  
03:07:35 25 50 percent of your RCC patients; correct?

George - Cross

03:07:37 1 A. Yes.

03:07:38 2 Q. And in that same time frame, both before and after  
03:07:42 3 Cabometyx was approved, you prescribed pazopanib to around  
03:07:47 4 30 percent of your RCC patients; true?

03:07:49 5 A. Roughly, yes.

03:07:51 6 Q. You showed us the NCCN guidelines, and so I'd like to  
03:07:54 7 pull those up at PTX-528.

03:07:58 8 MR. COOPER: Let's pull up the charts on Pages  
03:08:00 9 15 to 16.

03:08:00 10 BY MR. COOPER:

03:08:02 11 Q. And so, you talked to us about some of the  
03:08:07 12 recommended regimens here, do you recall that?

03:08:10 13 A. I do. Yes.

03:08:11 14 Q. And for first-line treatment of RCC, cabozantinib is  
03:08:16 15 not the only preferred regimen here; agreed?

03:08:18 16 A. Agreed.

03:08:18 17 Q. For instance, axitinib and pembrolizumab combo  
03:08:24 18 therapy is one of the preferred regimens; right?

03:08:27 19 A. Something like that, yes.

03:08:28 20 Q. Thank you.

03:08:28 21 And you prescribed that combo therapy as  
03:08:32 22 first-line therapy for both your favorable risk and your  
03:08:35 23 poor or intermediate risk patients; correct?

03:08:37 24 A. I have. Yes.

03:08:38 25 Q. And same thing with the lenvatinib and pembrolizumab

George - Cross

03:08:42 1 combination therapy; correct?

03:08:44 2 A. Yes, it's -- it's pembrolizumab.

03:08:47 3 Q. Thank you for that.

03:08:48 4 But what you also did is you highlighted, in the  
03:08:50 5 top -- the top box there, cabozantinib, and you pointed out  
03:08:54 6 that that's the only monotherapy that is a preferred -- down  
03:08:58 7 in the intermediate box is what we're highlighting. There,  
03:09:03 8 cabozantinib by itself is the only monotherapy that is  
03:09:07 9 available that is in the preferred regimens, you remember  
03:09:10 10 talking about that?

03:09:11 11 A. I'm with you, Bryce.

03:09:12 12 Q. Thank you. Thank you.

03:09:13 13 But for most of your RCC patients, you don't  
03:09:17 14 prescribe cabozantinib as monotherapy for first-line  
03:09:21 15 treatment; correct?

03:09:22 16 A. Yeah, that -- that's really for patients who are not  
03:09:25 17 eligible or can't tolerate immunotherapy. We have patients  
03:09:30 18 with severe autoimmune diseases and whatnot. And  
03:09:32 19 cabozantinib there fills a really important unmet need.

03:09:35 20 Q. Sure. But I'm saying that you've got a list of  
03:09:37 21 preferred regimens, and for most of your patients, you don't  
03:09:40 22 prescribe cabozantinib as monotherapy for first-line  
03:09:43 23 treatment; is that correct?

03:09:44 24 A. That's correct.

03:09:45 25 Q. And then looking at the other recommend regimens

George - Cross

03:09:48 1 there are drugs like pazopanib and sunitinib, those are  
03:09:51 2 other TKIs that are listed for first-line treatment;  
03:09:54 3 correct?

03:09:54 4 A. Yes.

03:10:00 5 Q. And then in the subsequent line therapy chart, you  
03:10:05 6 see that cabozantinib is one of the recommended regimens for  
03:10:10 7 prior IO therapy patients; correct?

03:10:13 8 A. Yes.

03:10:13 9 Q. And -- but there are three other TKIs in there -- or  
03:10:17 10 three other regimens in there as well; correct?

03:10:19 11 A. Yes.

03:10:21 12 Q. And for patients in that category, you prescribe each  
03:10:26 13 of those regimens to your patients in that category;  
03:10:28 14 correct?

03:10:29 15 A. Yes.

03:10:31 16 Q. Okay. You mentioned the CABOSUN trial, and that's  
03:10:34 17 the trial that compared cabozantinib against sunitinib in  
03:10:39 18 first line -- for first-line RCC treatment; right?

03:10:42 19 A. That's correct.

03:10:43 20 Q. Now -- and you were involved in that trial right?

03:10:45 21 A. Yes, yes.

03:10:47 22 Q. There's never been a head-to-head study comparing  
03:10:50 23 overall survival or progression-free survival for  
03:10:55 24 cabozantinib versus any other TKI drug other than sunitinib;  
03:11:00 25 correct?



George - Cross

03:11:00 1 A. That's true.

03:11:02 2 Q. And so you aren't offering an opinion that Cabometyx  
03:11:04 3 has been shown to be more effective than pazopanib, for  
03:11:09 4 instance, for first-line RCC treatment; right?

03:11:12 5 A. Yeah, I -- you know, I would just say that, you know,  
03:11:15 6 on -- on my own experience, and based on the fact that  
03:11:19 7 pazopanib, or what we call pazopanib, had been studied  
03:11:24 8 head-to-head against sunitinib in a large Phase 3 study, and  
03:11:28 9 demonstrated no difference between those two agents that --  
03:11:32 10 like we do often in cancer.

03:11:34 11 And we have to pick a treatment without Level 1  
03:11:37 12 head-to-head evidence that extrapolate -- extrapolate from  
03:11:41 13 that data to say that cabozantinib was superior to sunitinib  
03:11:46 14 in the setting. And there's no other agent that's superior  
03:11:50 15 to sunitinib. So it's my treatment of choice for those  
03:11:53 16 patients in the front-line setting that can't receive  
03:11:55 17 immunotherapy.

03:11:56 18 Q. And, Doctor, I want to ask you about the opinions  
03:11:58 19 you're offering in this case, so if you could listen  
03:12:01 20 carefully?

03:12:01 21 A. Okay.

03:12:02 22 Q. You're not offering an opinion that Cabometyx has  
03:12:04 23 been shown to be more effective than pazopanib as first-line  
03:12:08 24 therapy for RCC; is that fair?

03:12:09 25 A. No, I'm not.

George - Cross

03:12:10 1 Q. And I don't think we mentioned, but the CABOSUN trial  
03:12:14 2 was performed only with the intermediate or poor risk  
03:12:18 3 patients population; correct?

03:12:20 4 A. That's correct.

03:12:21 5 Q. So there's actually never been any head-to-head study  
03:12:24 6 between Cabometyx and another TKI for RCC patients with  
03:12:28 7 favorable risk; correct?

03:12:30 8 A. The Cabometyx and nivolumab versus as sunitinib --

03:12:36 9 Q. I said monotherapy.

03:12:37 10 A. Oh, monotherapy. No, you're correct.

03:12:40 11 Q. But getting to the point -- your point, that  
03:12:42 12 Cabometyx has been now approved --

03:12:44 13 MR. COOPER: You can take that down. Thank you.

03:12:44 14 BY MR. COOPER:

03:12:45 15 Q. -- been approved for combination therapy with  
03:12:48 16 nivolumab as a first-line treatment for RCC; correct?

03:12:51 17 A. That's correct.

03:12:52 18 Q. And you mentioned the CheckMate trial, we put that up  
03:12:56 19 real quick. And that compared Cabometyx plus nivolumab  
03:13:01 20 versus sunitinib; correct?

03:13:03 21 A. That's correct.

03:13:04 22 Q. Now, the combination therapy aspect of that is  
03:13:07 23 important; right?

03:13:08 24 A. Absolutely.

03:13:09 25 Q. Right. Because the IO drug that's part of that

George - Cross

03:13:11 1 combination therapy has been instrumental in improving  
03:13:17 2 patient outcomes; correct?

03:13:19 3 A. Yes.

03:13:20 4 Q. There's no study testing the TKIs sunitinib or  
03:13:24 5 pazopanib in combination with nivolumab as first-line  
03:13:29 6 therapy to treat RCC; yes or no?

03:13:31 7 A. That's because they were not tolerated.

03:13:33 8 Q. Okay.

03:13:34 9 Is my question true?

03:13:35 10 A. Yes, it's true.

03:13:36 11 Q. Okay. So the CheckMate trial -- and, also, the  
03:13:39 12 CheckMate trial wasn't the first study that compared a TKI  
03:13:43 13 and an IO combo therapy against just a TKI monotherapy;  
03:13:48 14 right?

03:13:48 15 A. That's true.

03:13:49 16 Q. Right. So there have been pembrolizumab plus  
03:13:54 17 axitinib that had also been shown to be more effective than  
03:13:57 18 sunitinib alone; right?

03:13:58 19 A. Yes.

03:13:59 20 Q. And avelumab and axitinib, that had also been shown  
03:14:03 21 to be more effective than sunitinib alone; correct?

03:14:06 22 A. Yes.

03:14:07 23 Q. Okay. So, this wasn't particularly unusual when you  
03:14:11 24 take into account there were two others; right?

03:14:13 25 A. It has differences in outcomes that we can go into if

George - Cross

03:14:17 1 you like.

03:14:18 2 Q. Okay. Now, you also talked about the METEOR trial,  
03:14:25 3 you recall that?

03:14:25 4 A. Yes.

03:14:26 5 Q. You were involved in that trial, the working of that  
03:14:29 6 trial as well; correct?

03:14:30 7 A. That's true, yes.

03:14:31 8 Q. And that one was where cabozantinib was tested  
03:14:33 9 against everolimus -- you know, I did better in these in  
03:14:37 10 your deposition -- cabozantinib versus everolimus?

03:14:41 11 A. Yes.

03:14:41 12 Q. And that was for second-line treatment; correct?

03:14:43 13 A. It was in subsequent --

03:14:45 14 Q. Subsequent line?

03:14:46 15 A. -- yeah, so one or more prior TKIs.

03:14:48 16 Q. And your -- other than with everolimus, there's never  
03:14:53 17 been any head-to-head trials between Cabometyx and any other  
03:14:56 18 TKI as subsequent-line RCC treatment; correct?

03:14:59 19 THE WITNESS: That's true.

03:15:01 20 Q. And you agree that other TKIs, like sunitinib and  
03:15:05 21 sorafenib, have also been shown to successfully treat RCC  
03:15:09 22 patients; correct?

03:15:10 23 A. Only in the front-line setting.

03:15:12 24 Q. All right. And you also showed us real quick the  
03:15:16 25 CONTACT-03 trial. Do you recall that?

George - Cross

03:15:18 1 A. I do.

03:15:19 2 Q. And that was the trial where the cabozantinib combo  
03:15:25 3 therapy performed about as well as the cabozantinib  
03:15:29 4 monotherapy; right?

03:15:30 5 A. Yes.

03:15:44 6 Q. Doctor, one of your opinions on objective indicia is  
03:15:48 7 that Cabometyx is "a clinical success." That's what you've  
03:15:51 8 termed it; right?

03:15:52 9 A. Yes.

03:15:53 10 Q. And you formed an opinion on this subject because you  
03:15:55 11 received an instruction that quote/unquote clinical success  
03:16:00 12 can serve as objective evidence of non-obviousness of a  
03:16:03 13 patent. That's why you did that; right?

03:16:04 14 A. Well, I was asked to speak on the clinical success of  
03:16:08 15 this drug. I --

03:16:09 16 Q. Okay.

03:16:09 17 A. -- I didn't make it up. It's real.

03:16:11 18 Q. Right. What I'm saying is that the reason you're  
03:16:13 19 talking about it today is because you were instructed that  
03:16:15 20 is an actual objective indicia.

03:16:17 21 A. Yes.

03:16:17 22 Q. Okay. Now, cabozantinib does not improve clinical  
03:16:21 23 outcomes for all patients it's prescribed to; correct?

03:16:24 24 A. Absolutely. No drug does.

03:16:26 25 Q. And we can agree that RCC patients develop a

George - Cross

03:16:31 1 resistance to cabozantinib; correct?

03:16:33 2 A. Most do.

03:16:35 3 Q. Yeah. And they -- just like other TKIs; right?

03:16:37 4 A. Absolutely, yeah.

03:16:38 5 Q. Some patients cannot tolerate Cabometyx; is that  
03:16:41 6 true?

03:16:41 7 A. That's true.

03:16:42 8 Q. And Cabometyx has a similar toxicity profile to other  
03:16:46 9 TKIs; correct?

03:16:47 10 A. Yes.

03:16:48 11 Q. You -- very briefly, you mentioned that Cabometyx had  
03:16:53 12 received FDA -- had been designated as a breakthrough  
03:16:58 13 therapy by FDA; is that right?

03:17:00 14 A. Yes.

03:17:00 15 Q. And that's a regulatory designation that the FDA  
03:17:05 16 gives to certain drugs in development; is that true?

03:17:08 17 A. That's true.

03:17:09 18 Q. And but the definition for giving that breakthrough  
03:17:14 19 therapy designation is that it's for a drug that treats a  
03:17:17 20 serious or life-threatening condition; correct?

03:17:19 21 A. That's right.

03:17:20 22 Q. And we can agree that cancer is a serious or  
03:17:22 23 life-threatening condition; right?

03:17:24 24 A. Yes, but not all cancer therapies get breakthrough.

03:17:27 25 Q. I understand that, but that's -- that then allows

George - Cross

03:17:31 1 accelerated review by the FDA of the drug; correct?

03:17:34 2 A. Yes.

03:17:35 3 Q. Okay. You're -- shifting to just two questions  
03:17:42 4 about: You're familiar with MSN's expert, Dr. Mega;  
03:17:46 5 correct?

03:17:46 6 A. Yes.

03:17:46 7 Q. You consider him a respected researcher in the  
03:17:48 8 oncology field as well; yes?

03:17:50 9 A. I do.

03:17:51 10 Q. You mentioned at the end of your testimony a few  
03:17:56 11 opinions about genotoxicity. Do you recall that?

03:17:59 12 A. I do.

03:18:00 13 Q. You agree that in formulating a drug product, a  
03:18:03 14 research team is motivated to avoid or minimize genotoxic  
03:18:08 15 impurities as much as possible; correct?

03:18:10 16 A. Yes.

03:18:11 17 Q. And genotoxic impurities can, as I think you said,  
03:18:13 18 increase the chances of lifetime risks of secondary cancer;  
03:18:17 19 correct?

03:18:17 20 A. That's right.

03:18:18 21 Q. And regulatory agencies, I think you also said, such  
03:18:21 22 as the FDA, provide guidelines for limits of genotoxic  
03:18:26 23 impurities in drug substances and products; right?

03:18:29 24 A. Yes.

03:18:29 25 Q. And a research team who's developing a drug, they're

Tate - Direct

03:18:32 1 motivated to prepare a drug product under those FDA limits  
03:18:36 2 when possible; correct?

03:18:37 3 A. Sure.

03:18:38 4 MR. COOPER: No further questions. Thank you.

03:18:40 5 MS. WIGMORE: No redirect, Your Honor.

03:18:41 6 THE COURT: All right. Dr. George, thank you.

03:18:43 7 Watch your step stepping down.

03:18:45 8 All right. So why don't we take the break until  
03:18:50 9 25 minutes of 4:00.

03:18:51 10 All right?

03:18:53 11 DEPUTY CLERK: All rise.

03:18:56 12 (Recess was taken.)

03:34:02 13 DEPUTY CLERK: All rise.

03:34:14 14 THE COURT: All right. Let's be seated and --

03:34:17 15 MS. PIROZZOLO: Plaintiffs call Michael Tate.

03:34:18 16 THE COURT: Okay. Tate.

03:34:30 17 DEPUTY CLERK: Please state and spell your full  
03:34:32 18 name for the record.

03:34:32 19 THE WITNESS: It's Michael, M-I-C-H-A-E-L, Tate,  
03:34:36 20 T-A-T-E.

03:34:37 21 MICHAEL TATE, the witness herein, after having  
03:34:37 22 been duly affirmed under oath, was examined and testified as  
03:34:37 23 follows:

03:34:50 24 DIRECT EXAMINATION

03:34:50 25 BY MS. PIROZZOLO:



Tate - Direct

03:34:52 1 Q. Good afternoon, could you please introduce yourself?

03:34:54 2 A. Good afternoon my name is Mike Tate.

03:34:57 3 Q. Mr. Tate, have you been retained by Exelixis as an  
03:35:01 4 expert in this case?

03:35:02 5 A. I have, yes.

03:35:03 6 Q. What issues have you been asked to address?

03:35:05 7 A. So, I'm going to discuss the commercial success of  
03:35:08 8 the cabozantinib products and in particular Cabometyx.

03:35:12 9 MS. PIROZZOLO: Let's put Plaintiff's  
03:35:13 10 Demonstrative Exhibit 8 on the screen and go to Slide 2.

03:35:13 11 BY MS. PIROZZOLO:

03:35:20 12 Q. What is your educational background?

03:35:22 13 A. So I about have a BBA in finance. That is a bachelor  
03:35:26 14 of business administration degree from the University of  
03:35:28 15 Houston. And then I entered -- upon graduating from U of H,  
03:35:32 16 I entered the Krannert School of Management at Purdue  
03:35:36 17 University where I received a master of science in  
03:35:39 18 industrial administration degree which is similar to an MBA.

03:35:42 19 Q. Where do you work?

03:35:43 20 A. I am a vice president in the intellectual property  
03:35:48 21 practice of Charles River Associates. Charles River  
03:35:51 22 Associates is an economic business consulting firm.

03:35:54 23 Q. And what is the nature of your work at Charles River  
03:36:00 24 Associates?

03:36:00 25 A. So most of what I do involves the preparation of

Tate - Direct

03:36:03 1 financial and economic analyses for the purpose of  
03:36:05 2 determining damages or assessing commercial success in  
03:36:09 3 patent infringement cases.

03:36:10 4 Q. Okay.

03:36:11 5 MS. PIROZZOLO: Let's put Plaintiff's Exhibit  
03:36:13 6 778 on the screen, and that's Tab 1 in your binder.

03:36:17 7 Q. Could you identify Exhibit 778?

03:36:20 8 A. Sure. This is my current CV.

03:36:23 9 Q. Does this exhibit provide an accurate summary of your  
03:36:27 10 education and professional experience?

03:36:31 11 A. It does, yes.

03:36:33 12 MS. PIROZZOLO: Your Honor, Exelixis offers  
03:36:34 13 Mr. Tate as an expert in the field of economic analysis as  
03:36:39 14 it pertains to commercial success.

03:36:42 15 MS. GRDEN: No objection.

03:36:42 16 THE COURT: All right. You may proceed.

03:36:44 17 BY MS. PIROZZOLO:

03:36:46 18 Q. Did you focus on any particular product in your  
03:36:50 19 analysis of commercial success?

03:36:51 20 A. So I looked at both products, Cometriq and Cabometyx,  
03:36:54 21 but for purposes of today, I'm going to focus on Cabometyx,  
03:36:57 22 which represents about 95 percent of the revenue that  
03:37:01 23 Exelixis has generated from the sale of the cabozantinib  
03:37:04 24 products.

03:37:07 25 Q. Do the Cabometyx tablets practice each of the four

Tate - Direct

03:37:10 1 asserted patents?

03:37:11 2 A. That's my understanding. Yes.

03:37:13 3 Q. At a high level what did you conclude with regard to  
03:37:16 4 commercial success?

03:37:17 5 A. So based on the analyses that I did, I determined  
03:37:20 6 that the Cabometyx product was a commercial success.

03:37:24 7 MS. PIROZZOLO: Let's pull up Slide 3,  
03:37:28 8 Plaintiff's Demonstrative 8.3.

03:37:28 9 BY MS. PIROZZOLO:

03:37:30 10 Q. Could you explain the factors that you considered in  
03:37:33 11 your analysis?

03:37:34 12 A. So, I did a number of different analyses. First, I  
03:37:38 13 determined the number of patients treated with the  
03:37:41 14 cabozantinib products. Then I identified and analyzed the  
03:37:45 15 relevant markets for Cabometyx. And then within each of  
03:37:49 16 those markets, I looked at various measures of market share,  
03:37:53 17 and then lastly I determined the amount of revenue that  
03:37:56 18 Exelixis generated from the sale of the product in the U.S.  
03:37:59 19 marketplace.

03:38:01 20 MS. PIROZZOLO: Let's turn to Plaintiff's  
03:38:03 21 Exhibit 824 which is Tab 2 in your binder.

03:38:03 22 BY MS. PIROZZOLO:

03:38:08 23 Q. Could you describe what Plaintiff's Exhibit 824  
03:38:12 24 shows?

03:38:12 25 A. Sure. So, this is an internal Exelixis business

Tate - Direct

03:38:16 1 record. And this shows the cumulative number of patients  
03:38:19 2 treated by quarter with the cabozantinib product. And if I  
03:38:24 3 could focus everyone on the last bar on the right-hand side,  
03:38:28 4 that represents the number of patients treated in total as  
03:38:33 5 of about the end of April 2023. And you can see at the very  
03:38:37 6 top of the bar, there were approximately 55,000 patients  
03:38:41 7 treated with the cabozantinib products over the course of  
03:38:44 8 the products' life cycle.

03:38:46 9 Q. Now, one of the indications for Cabometyx is renal  
03:38:54 10 cell carcinoma; is that right?

03:38:55 11 A. That's correct. Yes.

03:38:57 12 Q. What percentage of Cabometyx prescriptions are for  
03:39:01 13 renal cell carcinoma?

03:39:02 14 A. So depending on the time period, it varies a bit, but  
03:39:07 15 I think greater than 92 or 93 percent of the patients of the  
03:39:11 16 usage is in the RCC segment of the marketplace. So that's  
03:39:15 17 the largest segment of use.

03:39:17 18 MS. PIROZZOLO: Let's put Plaintiff's  
03:39:20 19 Exhibit 823 on the screen, which is Tab 4 in your binder,  
03:39:25 20 and direct your attention to the second page of the exhibit  
03:39:29 21 on the right-hand side.

03:39:31 22 THE WITNESS: Okay.

03:39:31 23 BY MS. PIROZZOLO:

03:39:31 24 Q. What does this page show?

03:39:32 25 A. So, this again, is an internal Exelixis business

Tate - Direct

03:39:36 1 record, and this shows the TRX share of a market called  
03:39:44 2 CISVL.

03:39:44 3 And the CISVL is the acronym, Your Honor, for  
03:39:48 4 the products that you see listed in the key. Each one of  
03:39:52 5 those products is in this particular marketplace. And those  
03:39:55 6 products are in this marketplace because they are all TKIs  
03:40:00 7 or tyrosine kinase inhibitors. And so this is one way that  
03:40:04 8 Exelixis monitors the market for Cabometyx and the  
03:40:08 9 performance of Cabometyx.

03:40:09 10 Q. Okay. And does this graph pertain to certain  
03:40:13 11 indications for Cabometyx?

03:40:14 12 A. Yes. My understanding is this relates to the RCC  
03:40:18 13 indication in the U.S. marketplace.

03:40:22 14 Q. What did you learn about the market share of  
03:40:24 15 Cabometyx based on the data in exhibit -- Plaintiff's  
03:40:28 16 Exhibit 823?

03:40:28 17 A. So, if we could focus on the bottom of the chart,  
03:40:33 18 you'll see the blue shaded areas. Each one of these bars is  
03:40:37 19 the quarterly -- represents quarterly market shares. And  
03:40:40 20 you can see that the blue shaded area, that's Cabometyx.  
03:40:43 21 And we -- if we look at the left-hand bar -- the very  
03:40:47 22 left-hand bar, you see in Quarter 3 of 2020, Cabometyx's  
03:40:51 23 share in this particular market segment was 26 percent.

03:40:55 24 Now, that share grew a quarter -- over the  
03:40:58 25 quarter until we get out into the 2022 time frame and it

Tate - Direct

03:41:02 1 maintained itself at about 39 percent, beginning of the  
03:41:07 2 fourth quarter of 2022 into the first two quarters of 2023.

03:41:12 3 And as we can see, in this particular segment of  
03:41:15 4 the market, Cabometyx has achieved market leadership  
03:41:19 5 position in terms of TRxs and a TRx is the total number of  
03:41:24 6 prescriptions written in the marketplace. So Cabometyx has  
03:41:26 7 a 39 percent share of that marketplace relative to the other  
03:41:29 8 TKIs in the market.

03:41:30 9 Q. Was Cabometyx the first tyrosine kinase inhibitor  
03:41:34 10 approved for the treatment of renal cell carcinoma?

03:41:38 11 A. It was not. It was the third or fourth product which  
03:41:42 12 received approval in that marketplace. So it was able to  
03:41:45 13 achieve these shares in spite of competition from products  
03:41:48 14 that existed in the marketplace prior to its launch in 2016.

03:41:52 15 Q. How, if at all, does that impact your analysis of  
03:41:55 16 commercial success?

03:41:56 17 A. Well, it shows me -- it's an indicator of commercial  
03:41:59 18 success given that Cabometyx was able to grow and then  
03:42:02 19 maintain its share and become the market leader.

03:42:06 20 Q. Now, we've been discussing a comparison of Cabometyx  
03:42:10 21 to other tyrosine kinase inhibitors. Did you also look at  
03:42:15 22 Cabometyx's share of the broader market for renal cell  
03:42:19 23 carcinoma treatments?

03:42:21 24 A. I did. Yes.

03:42:22 25 MS. PIROZZOLO: Let's put up Plaintiff's

Tate - Direct

03:42:23 1 Demonstrative 8.4.

03:42:23 2 BY MS. PIROZZOLO:

03:42:26 3 Q. What does this chart show?

03:42:29 4 A. So this charts reflects the overall RCC market and  
03:42:33 5 it's based on what's called new patient share. And I've  
03:42:37 6 pictured on the chart at the top, I think, nine products in  
03:42:41 7 the marketplace, but there are, depending on the time frame,  
03:42:45 8 13 to 16 total products in the marketplace. But I put the  
03:42:48 9 top nine performers on the chart that you see here.

03:42:51 10 And so, this reflects the market shares of these  
03:42:56 11 products from Quarter 4 of 2019 through Quarter 4, 2022.  
03:43:02 12 And Cabometyx is found in two places on this chart, it's  
03:43:06 13 reflected in two places.

03:43:07 14 One is the solid red line, which is about -- if  
03:43:10 15 you look at about halfway down the chart, you see the solid  
03:43:13 16 red line. That's the share for Cabometyx in the overall RCC  
03:43:16 17 market when used as a monotherapy, so when used alone. And  
03:43:20 18 you can see that during the first half of the period  
03:43:23 19 reflected here, the share varied between 10 and 15 percent.  
03:43:27 20 And then that share grew in the latter half of the period to  
03:43:31 21 the 15 to 20 percent range.

03:43:34 22 Now, the second place that we need to focus on  
03:43:37 23 is the dashed red line, which is toward the bottom of the  
03:43:41 24 chart. That is the market share Cabometyx used in  
03:43:46 25 combination with Opdivo, that's the combination product. As

Tate - Direct

03:43:51 1 you can see in the first half of the period, the share  
03:43:54 2 varied between 1 and 4 percent and then it increased to the  
03:44:00 3 5 to 8 percent range in the latter half of the chart.

03:44:04 4 Now, Cabometyx used a monotherapy, you can see  
03:44:07 5 ranked second or third in the marketplace, depending on the  
03:44:10 6 quarter that we're looking at. But if you add the two  
03:44:14 7 usages together, the monotherapy with the combination  
03:44:17 8 product, you would find that in the latter period, in the  
03:44:21 9 2022 period, Cabometyx became the market leader.

03:44:25 10 MS. PIROZZOLO: Now, let's put up Plaintiff's  
03:44:27 11 Demonstrative Exhibit 8.5.

03:44:27 12 BY MS. PIROZZOLO:

03:44:30 13 Q. Could you explain what this chart shows?

03:44:32 14 A. Sure. So this is a similar chart and it is -- except  
03:44:38 15 it's not the overall market. Now, we're looking at the  
03:44:40 16 second line segment of the market and we heard Dr. George  
03:44:43 17 explain what -- what second-line therapy meant during his  
03:44:46 18 testimony. But here, again, we focus on two lines. One is  
03:44:52 19 the very top line that is the solid red line, that's  
03:44:56 20 Cabometyx used as a monotherapy. And you can see here that  
03:44:59 21 the share varied depending on the quarter between 20 percent  
03:45:03 22 and 35 percent. But Cabometyx was the clear market leader,  
03:45:07 23 even if we only look at the monotherapy alone.

03:45:11 24 But let's also focus then on the -- on the  
03:45:15 25 bottom of the chart where the dashed red line is. That,



Tate - Direct

03:45:19 1 again, reflects Cabometyx used in combination with Opdivo.

03:45:23 2 And there we can see the share varied depending on the

03:45:26 3 quarter between 2 and 5 or 6 percent. And so, in the

03:45:30 4 second-line therapy, Cabometyx was the clear market leader

03:45:35 5 throughout the time frame that we're looking at here.

03:45:40 6 Q. Now, did you also look at the revenue for Cabometyx?

03:45:43 7 A. I did. Yes.

03:45:45 8 MS. PIROZZOLO: Okay. Let's put Plaintiff's

03:45:47 9 Demonstrative Exhibit 8.6 up.

03:45:47 10 BY MS. PIROZZOLO:

03:45:51 11 Q. Can you describe what is shown here?

03:45:53 12 A. Sure. So, this is a chart that reflects the annual

03:45:58 13 net product revenue for the Cabometyx product sold in the

03:46:02 14 U.S. We start in 2016, which was the launch year, and we

03:46:09 15 see that year over year there was growth in net revenue in

03:46:14 16 the U.S. marketplace. And we get to 2022 and we see

03:46:18 17 approximately \$1.4 billion of revenue for 2022. So, pretty

03:46:24 18 significant growth between the launch in 2016 and -- and the

03:46:28 19 most recent four-year data that we had in 2022.

03:46:32 20 Now, in total, for this time frame, there was

03:46:36 21 \$4.9 billion of revenue generated in the U.S. market by

03:46:41 22 Exelixis from the sale of Cabometyx.

03:46:45 23 Q. What sources did you use to prepare the summary of

03:46:47 24 revenue on PDX-8.6?

03:46:51 25 A. Yeah. So this -- this source here is PTX-802, which

Tate - Direct

03:46:56 1 is the profit and loss statement for Cabometyx. It's  
03:47:01 2 Exelixis' internal accounting document.

03:47:04 3 Q. Mr. Tate, do you have an understanding of whether  
03:47:06 4 there is a nexus between the commercial success of Cabometyx  
03:47:09 5 and the asserted claims?

03:47:10 6 A. I do. Yes.

03:47:12 7 Q. In summary, what did you -- and what is that  
03:47:15 8 understanding?

03:47:16 9 A. So, my understanding, the way I look at nexus in this  
03:47:20 10 case is I'm relying on the technical experts for the  
03:47:22 11 clinical benefits that -- the technical benefits that the  
03:47:26 12 product provides. It's those benefits that contribute to  
03:47:30 13 the clinical success that you heard Dr. George speak of.  
03:47:34 14 The clinical benefits then drive Dr. George, or oncologists  
03:47:37 15 like him, to prescribe the product to the relevant patient  
03:47:40 16 group. Not all patients, but the relevant patient group.  
03:47:43 17 Those prescriptions when filled, then generate the revenues  
03:47:46 18 and market shares that you saw on the slides that I  
03:47:49 19 presented here today. And so, there's a direct link between  
03:47:53 20 the technical aspects, the claims of the patent, and the  
03:47:55 21 revenue that is generated.

03:47:59 22 MS. PIROZZOLO: Thank you, Mr. Tate.

03:48:01 23 Your Honor, we would like to move the following  
03:48:05 24 exhibits used with Mr. Tate into evidence: Plaintiff's  
03:48:09 25 Exhibit 778, Plaintiff's Exhibit 824, Plaintiff's

Tate - Cross

03:48:14 1 Exhibit 823, Plaintiff's Exhibit 791, Plaintiff's Exhibit  
03:48:21 2 853, and Plaintiff's Exhibit 802.

03:48:23 3 MS. GRDEN: No objection.

03:48:24 4 THE COURT: All right. Admitted without  
03:48:26 5 objection.

03:48:10 6 (PTX Exhibit Nos. 778, 791, 802, 823, 824, 853,  
03:48:22 7 were admitted into evidence.)

03:48:28 8 THE COURT: Thank you.

03:48:29 9 MS. GRDEN: We'll pass up some cross binders,  
03:48:42 10 Your Honor, with your permission.

03:48:45 11 THE COURT: Yeah.

03:49:05 12 CROSS-EXAMINATION

03:49:07 13 BY MS. GRDEN:

03:49:07 14 Q. Good afternoon, Mr. Tate. Nice to see you again.

03:49:12 15 A. Good afternoon.

03:49:14 16 Q. Mr. Tate, the last question that your counsel asked  
03:49:16 17 you was whether or not there is a nexus to the claimed  
03:49:19 18 invention of the patents in this case; right?

03:49:20 19 A. That's correct.

03:49:21 20 Q. You opine that there is; yes?

03:49:22 21 A. That's correct.

03:49:24 22 Q. You've opined on the commercial success of Cabometyx  
03:49:27 23 before this case; right?

03:49:28 24 A. I did. Yes.

03:49:29 25 Q. That was the case that we have been calling

Tate - Cross

03:49:32 1 Cabozantinib 1 case?

03:49:33 2 A. And MSN 1 or -- yes. That's correct.

03:49:34 3 Q. And one of the patents at issue there was the  
03:49:36 4 '473 patent that we've also heard a bit about during this  
03:49:39 5 case?

03:49:39 6 A. Correct. It was.

03:49:40 7 Q. And in that case you said there was a nexus between  
03:49:43 8 the '473 patent and Cabometyx; correct?

03:49:45 9 A. I said in part, yes. That part of the success was  
03:49:48 10 attributable to that patent, yes.

03:49:50 11 Q. Well, in fact, you concluded that the -- that  
03:49:53 12 Cabometyx was a commercial success and that the success was  
03:49:56 13 attributable to Claim 5 of the '473 patent; correct?

03:50:00 14 A. That's correct.

03:50:01 15 Q. And you went a little bit further. Isn't it right  
03:50:03 16 that you testified in Court there was a direct roadmap from  
03:50:07 17 Claim 5 of the '473 patent to revenue generation for  
03:50:11 18 Cabometyx; correct?

03:50:12 19 A. That's correct. All of these patents in combination  
03:50:14 20 work together. So, yes. That is correct.

03:50:18 21 MS. GRDEN: Thank you.

03:50:19 22 No further questions.

03:50:19 23 THE COURT: All right. Mr. Tate, you can step  
03:50:23 24 down.

03:50:24 25 Right? There's nothing more?

Mega - Direct

03:50:25 1 MS. PIROZZOLO: Plaintiff's rest, Your Honor.

03:50:27 2 THE COURT: Okay. So, watch your step.

03:50:29 3 THE WITNESS: Thank you.

03:50:30 4 THE COURT: All right. Defendant?

03:50:39 5 MR. COOPER: MSN calls Dr. Anthony Mega.

03:50:52 6 DEPUTY CLERK: Please state and spell your full  
03:51:07 7 name for the record.

03:51:07 8 THE WITNESS: Yes. Anthony Emmanuel Mega.

03:51:12 9 A-N-T-H-O-N-Y, E-M-M-A-N-U-E-L, M-E-G-A.

03:51:12 10 ANTHONY MEGA, the witness herein, after having  
03:51:12 11 been duly sworn under oath, was examined and testified as  
03:51:12 12 follows:

03:51:12 13 THE WITNESS: I do.

03:51:45 14 MR. COOPER: May it please the Court?

03:51:46 15 DIRECT EXAMINATION

03:51:46 16 BY MR. COOPER:

03:51:47 17 Q. Good morning. Could you please introduce yourself to  
03:51:49 18 the Court?

03:51:49 19 A. Yes. I'm Anthony Mega, M.D.

03:51:53 20 Q. Dr. Mega, have you prepared slides to assist in your  
03:51:56 21 testimony today?

03:51:56 22 A. Yes, I did.

03:51:57 23 Q. For the record, those slides are on the screen marked  
03:52:01 24 in the bottom right-hand corner as DDX Mega, and then the  
03:52:04 25 slide number.

Mega - Direct

03:52:05 1 MR. COOPER: Could we please pull up DTX-536,  
03:52:10 2 and call out the second page.

03:52:10 3 BY MR. COOPER:

03:52:11 4 Q. Dr. Mega, could you please identify this exhibit?

03:52:14 5 A. Yes. This is my curriculum vitae dated June 2023.

03:52:18 6 Q. Does it accurately reflect your employment  
03:52:21 7 credentials and education?

03:52:22 8 A. Yes, it does.

03:52:23 9 MR. COOPER: Can we turn to Slide DDX 2.

03:52:26 10 BY MR. COOPER:

03:52:26 11 Q. Dr. Mega, are you a board certified physician?

03:52:28 12 A. Yes. I am board certified in medical oncology.

03:52:32 13 Q. How long have you been practicing in the field of  
03:52:34 14 medical oncology?

03:52:35 15 A. Nearly 30 years.

03:52:38 16 Q. Can you please briefly describe your current  
03:52:40 17 employment?

03:52:40 18 A. I'm a associate professor of medicine at Brown  
03:52:46 19 University. My clinical practice is via the Lifespan Cancer  
03:52:53 20 Institute. I'm employed by Brown Physicians, Incorporated,  
03:52:56 21 as part of that practice. So I'm medical director of  
03:53:02 22 genitourinary oncology within that group and I direct the  
03:53:06 23 multidisciplinary clinics in genitourinary oncology. I'm a  
03:53:11 24 staff oncologist practicing at the Lifespan Cancer  
03:53:15 25 Institute.

Mega - Direct

03:53:15 1 Q. So as part of your work, do you treat and -- see and  
03:53:19 2 treat cancer patients?

03:53:20 3 A. Yes, I do.

03:53:20 4 Q. Have you published any articles over the course of  
03:53:23 5 your career?

03:53:24 6 A. Yes, I have. I've published over 50 peer-reviewed  
03:53:29 7 articles and over 20 abstracts.

03:53:33 8 Q. Approximately how many times have you given testimony  
03:53:35 9 as an expert in the field of medical oncology?

03:53:38 10 A. I would say approximately 20 times.

03:53:41 11 MR. COOPER: Your Honor, defendants proffer  
03:53:42 12 Dr. Anthony Mega as an expert in the field of medical  
03:53:45 13 oncology.

03:53:47 14 MS. WIGMORE: No objection.

03:53:47 15 THE COURT: All right. You may proceed.

03:53:49 16 MR. COOPER: Thank you. You can take that down.

03:53:49 17 BY MR. COOPER:

03:53:52 18 Q. Dr. Mega, have you reviewed the four patents-in-suit  
03:53:54 19 in this case?

03:53:55 20 A. Yes, I have.

03:53:56 21 Q. Have you reviewed the claims that Exelixis has  
03:53:59 22 asserted against MSN?

03:54:00 23 A. I have.

03:54:02 24 Q. Were you present in Court and did you hear the entire  
03:54:04 25 testimony of Exelixis' expert Dr. George?

Mega - Direct

03:54:07 1 A. I have.

03:54:09 2 Q. Have you been engaged by MSN to provide opinions on  
03:54:12 3 certain objective indicia related to those asserted claims,  
03:54:16 4 namely long-felt and unmet need and what Dr. George has  
03:54:21 5 termed clinical success?

03:54:22 6 A. Yes.

03:54:24 7 Q. All right. Let's start with your brief background  
03:54:27 8 discussion. Dr. Mega, we've heard this term before, but can  
03:54:30 9 you please briefly describe what a tyrosine kinase is?

03:54:34 10 A. Yes. A tyrosine kinase is an enzyme that regulates  
03:54:43 11 cell growth through signal transduction. So, it will bind  
03:54:48 12 to proteins ligands, get -- get turned on. And then  
03:54:54 13 subsequently signal the cells to either proliferate,  
03:54:58 14 differentiate, turndown, program cell death, increase cell  
03:55:04 15 growth.

03:55:05 16 Q. What is the relationship between tyrosine kinases and  
03:55:08 17 cancer development?

03:55:09 18 A. Well, tyrosine kinases themselves are normal --  
03:55:14 19 regulate normal functioning cells. But there are certain  
03:55:18 20 mutations that can occur that turn on these tyrosine kinases  
03:55:23 21 and don't allow them to get turned off, would be one example  
03:55:27 22 of such mutation.

03:55:29 23 In that situation, you get dysregulated cell  
03:55:32 24 growth, which we -- often then would lead to malignant or  
03:55:36 25 cancerous situations.



Mega - Direct

03:55:38 1 Q. What are tyrosine kinase inhibitors or TKIs?

03:55:41 2 A. Tyrosine kinase inhibitors block this activation of  
03:55:48 3 tyrosine kinases through pathways such as phosphorylation.

03:55:53 4 Q. We've heard from Dr. George that cabozantinib is a  
03:55:55 5 TKI. Had TKI drugs been developed to treat cancer before  
03:56:00 6 cabozantinib?

03:56:00 7 A. Yes, absolutely, yes.

03:56:02 8 MR. COOPER: Can we go to DDX-3?

03:56:02 9 BY MR. COOPER:

03:56:06 10 Q. What was the first TKI drug approved to treat cancer?

03:56:10 11 A. Yes, imatinib or the brand name Gleevec was the first  
03:56:15 12 TKI. This was launched in 2001. And it's indicated by, you  
03:56:20 13 know, what was really a momentous moment, even in my now  
03:56:25 14 increasingly lengthy career, which is this TIME magazine  
03:56:29 15 acknowledgment, that this represented a really profound  
03:56:34 16 advancement. It was new ammunition in cancer, just by the  
03:56:39 17 mechanism in which it worked for chronic myelogenous  
03:56:42 18 leukemia.

03:56:43 19 Q. How did imatinib compare to the previous ways of  
03:56:46 20 treating cancer?

03:56:49 21 A. Extraordinary first in efficacy. When you -- at that  
03:56:53 22 point in my career, I was taking care of patients with  
03:56:56 23 chronic myelogenous leukemia. And this was a situation  
03:57:00 24 where this was a uniformly lethal disease within a three to  
03:57:05 25 five-year period of time. And this -- this mechanism to

Mega - Direct

03:57:10 1 block tyrosine kinase pathways really led to a profound  
03:57:15 2 difference in regards to the outcomes for people with this  
03:57:19 3 leukemia. So, that -- the efficacy component was certainly  
03:57:23 4 one of the components. But there were others. It was an  
03:57:27 5 oral agent.

03:57:29 6 Q. As -- sorry.

03:57:29 7 A. So it was an oral therapy for leukemia which was, you  
03:57:33 8 know, one of the few oral therapies that you could  
03:57:36 9 effectively treat cancer with. And it had a much better  
03:57:41 10 side effect profile comparatively to chemotherapy.

03:57:45 11 Q. Were there in -- any other TKIs that were  
03:57:48 12 subsequently approved by FDA to treat cancer by 2009?

03:57:52 13 A. Yeah, I think the -- the advent of imatinib then just  
03:57:58 14 opened the door, and we had then another sequence of TKIs  
03:58:04 15 that subsequently were approved, which I have listed here.  
03:58:07 16 Gefitinib, erlotinib, sorafenib, dasatinib, sunitinib,  
03:58:14 17 lapatinib, nilotinib, and vandetanib.

03:58:19 18 Q. And we heard about each of these -- some of these  
03:58:21 19 drugs, I should say, are spectrum selective. Do you recall  
03:58:24 20 that testimony from Dr. George?

03:58:26 21 A. Yes.

03:58:27 22 Q. Can you remind us what that means?

03:58:29 23 A. Well, spectrum selective is a -- there are multiple  
03:58:34 24 pathways that -- tyrosine kinase pathways that these agents  
03:58:40 25 affect, with the exception of the -- of some of the

Mega - Direct

03:58:43 1 EGFR-specific agents. But -- so there were multiple  
03:58:47 2 pathways that can be affected by these tyrosine kinases.

03:58:50 3 Q. Does --

03:58:51 4 A. Inhibitors.

03:58:52 5 Q. And Dr. George mentioned that cabozantinib affects  
03:58:56 6 c-Met as one of its pathways, do you recall that?

03:58:58 7 A. Yes.

03:58:59 8 Q. Does each TKI pathway play a different role in tumor  
03:59:03 9 growth?

03:59:03 10 A. Well, the pathways themselves are distinct. But they  
03:59:11 11 often merge together into more prominent pathways that then  
03:59:17 12 influence cellular proliferation and growth, similar to,  
03:59:21 13 say, secondary roads leading into interstate highways.

03:59:25 14 Q. Okay.

03:59:25 15 MR. COOPER: Can you take that down. Thank you.

03:59:25 16 BY MR. COOPER:

03:59:27 17 Q. Dr. Mega, let's turn to your opinion regarding  
03:59:30 18 long-felt and unfelt need.

03:59:32 19 Can you please first just summarize for the  
03:59:34 20 Court the opinions you are going to testify about on that  
03:59:37 21 subject?

03:59:37 22 A. Yes. That cabozantinib did not meet a long-felt  
03:59:43 23 unmet need in the treatment of cancer, specifically the  
03:59:47 24 treatment of advanced renal cancer, or kidney cancer, and  
03:59:52 25 the treatment of advanced kidney cancer in combination with

Mega - Direct

03:59:55 1 immune checkpoint inhibitor.

03:59:57 2 Q. Now, has cabozantinib benefited individual RCC  
04:00:03 3 patients?

04:00:04 4 A. Oh, absolutely. They -- the drug has had a benefit  
04:00:11 5 for patients with advanced renal cell carcinoma, so there  
04:00:16 6 have been individual patients that have certainly benefited  
04:00:19 7 from it.

04:00:19 8 Q. In your opinion, does that clinical effect represent  
04:00:23 9 a difference in kind in the treatment of RCC?

04:00:26 10 A. It does not. I think it's an incremental improvement  
04:00:32 11 in therapy that represents a difference in degree.

04:00:36 12 Q. Okay. Can we go to -- you recall the two -- the  
04:00:47 13 indications that Dr. George referred to that Cabometyx  
04:00:51 14 treats; is that right?

04:00:51 15 A. Yes.

04:00:54 16 Q. Were there treatment options available for RCC,  
04:00:59 17 specifically, before cabozantinib received FDA approval for  
04:01:03 18 that indication?

04:01:04 19 A. Yes, there were -- there were numerous treatment  
04:01:08 20 options, several within that category of tyrosine kinase  
04:01:12 21 inhibitors.

04:01:13 22 Q. Were there any other categories of drugs that were --  
04:01:16 23 that treated RCC when Cabometyx -- or by 2009?

04:01:20 24 A. Yes. There was the angiogenic agent, bevacizumab.  
04:01:25 25 There were cytokine agents, such as alpha interferon and

Mega - Direct

04:01:31 1 interleukin, too. And there was also the mTOR inhibitors.

04:01:35 2 Q. Since FDA first approved cabozantinib to treat RCC,  
04:01:39 3 have there been new TKIs and other types of treatment that  
04:01:43 4 have entered the market?

04:01:44 5 A. Yes. The growth has continued on a steady pace in  
04:01:48 6 regards to newer tyrosine kinase inhibitors, and also the  
04:01:54 7 advent of the immune checkpoint inhibitors within this  
04:01:56 8 treatment space.

04:01:57 9 Q. Dr. George discussed the NCCN guidelines for kidney  
04:02:02 10 cancer. Do you use those as part of your practice as well?

04:02:04 11 A. I do use them as part of my practice in a similar way  
04:02:08 12 that Dr. George noted.

04:02:10 13 MR. COOPER: Can we please pull up PTX-528? And  
04:02:16 14 let's go to Page 15 and call out the chart. All right.

04:02:16 15 BY MR. COOPER:

04:02:21 16 Q. Do you discuss -- do you recall Dr. George discussing  
04:02:23 17 this chart?

04:02:24 18 A. Yes, I do.

04:02:25 19 Q. Could you describe what types of consensus  
04:02:28 20 recommendations are provided by these guidelines?

04:02:30 21 A. Yes. We can see these recommendations sort of listed  
04:02:35 22 as preferred regimens, other recommended regimens, and  
04:02:40 23 useful and in certain circumstances. And there are a  
04:02:44 24 variety of factors considered.

04:02:46 25 Q. What are the criteria used for determining what

Mega - Direct

04:02:49 1 category a treatment regimen is placed in by the NCCN  
04:02:53 2 guidelines?

04:02:53 3 A. Well, it's a consensus determination that takes into  
04:02:57 4 consideration efficacy, toxicity, maturation, you know,  
04:03:04 5 where the data is from a maturation standpoint,  
04:03:07 6 affordability.

04:03:09 7 Q. And so are there criteria related to things other  
04:03:12 8 than efficacy and safety that are taken into consideration?

04:03:16 9 A. Yes, there are.

04:03:18 10 Q. And Dr. George highlighted where cabozantinib falls  
04:03:21 11 on this chart. Are there other preferred and recommended  
04:03:24 12 options for treatment of RCC in each of the patient risk  
04:03:28 13 categories?

04:03:28 14 A. Yes, we can see a number of options. Principally,  
04:03:36 15 axitinib, lenvatinib, and cabozantinib being in combination  
04:03:40 16 with immune checkpoint inhibitor.

04:03:42 17 Q. And can you describe exactly what an immune  
04:03:44 18 checkpoint inhibitor is?

04:03:45 19 A. Sure. And immune checkpoint inhibitor is a class of  
04:03:53 20 agents that essentially turn the switch on for our immune  
04:03:58 21 system to detect and to use our own body's host defenses to  
04:04:05 22 kill cancer cells. And so it draws the curtain away from  
04:04:09 23 the cancer cells so our own immune system can be activated  
04:04:13 24 against it.

04:04:13 25 Q. Is there a preferred standard -- or is there a

Mega - Direct

04:04:15 1 standard of care for treatment of RCC today?

04:04:18 2 A. Yes. I think the standard of care today is that all  
04:04:22 3 patients that are appropriate should receive a combination  
04:04:26 4 of an immune checkpoint inhibitor plus a tyrosine kinase  
04:04:30 5 inhibitor.

04:04:31 6 Q. And Dr. George identified one of these combination  
04:04:35 7 therapies that includes cabozantinib. In your opinion, are  
04:04:39 8 any of the combination regimens in the preferred regimens  
04:04:42 9 category or poor intermediate category better than the  
04:04:47 10 others?

04:04:47 11 A. Even the consensus is that they're all on relatively  
04:04:54 12 equal footing. And in regards to these reg -- these  
04:04:58 13 combination regimens, they're either preferred regimens or  
04:05:03 14 other recommended regimens.

04:05:04 15 Q. We noticed that cabozantinib is a monotherapy that's  
04:05:07 16 in a poor intermediate risk group for a preferred regimen.  
04:05:12 17 Are physicians typically prescribing cabozantinib  
04:05:15 18 monotherapy for first-line treatment today?

04:05:18 19 A. Generally speaking, that first-line monotherapy is  
04:05:21 20 not being utilized today.

04:05:22 21 Q. And with regards to first-line RCC therapy, do you  
04:05:27 22 recall Dr. George testified about the Sunitinib trial?

04:05:30 23 A. Yes.

04:05:32 24 Q. Generally what did the CABOSUN study show?

04:05:34 25 A. Well, the CABOSUN trial was a randomized Phase II

Mega - Direct

04:05:39 1 study that looked at sunitinib versus cabozantinib as a  
04:05:46 2 first-line therapy for advanced renal cell carcinoma in  
04:05:52 3 previously untreated patients.

04:05:54 4 Q. And what did the -- and what did the results show?

04:05:57 5 A. Well, the results showed that there was a -- there  
04:06:01 6 was a statistically significant, albeit modest, difference  
04:06:05 7 in -- in progression-free survival, with cabozantinib being  
04:06:11 8 approximately eight and a half months to five and a half  
04:06:14 9 months for -- for sunitinib. But there was no overall  
04:06:19 10 survival benefit, because the study really wasn't designed  
04:06:24 11 to be powered to show a survival benefit.

04:06:26 12 Q. How did sunitinib perform in CABOSUN -- in the  
04:06:29 13 CABOSUN trial compared to other trials that had included  
04:06:34 14 sunitinib?

04:06:34 15 A. CABOSUN truly underperformed in this study, even if  
04:06:39 16 we -- if we look at other comparable studies in which  
04:06:44 17 sunitinib was used as a -- was used as the control arm, the  
04:06:51 18 progression-free survival rates were much better than what  
04:06:54 19 it showed in the CABOSUN trial.

04:06:55 20 Q. Now, cabozantinib has also been tested in combination  
04:06:59 21 with nivolumab against sunitinib. Did you hear Dr. George's  
04:07:04 22 testimony about the CheckMate study?

04:07:06 23 A. Yes, I did.

04:07:09 24 Q. And, again, what type of drug is nivolumab?

04:07:11 25 A. That's one of those immune checkpoint inhibitors.



Mega - Direct

04:07:14 1 Q. Was the check point -- CheckMate study -- if I said  
04:07:17 2 check point, I apologize -- CheckMate study the first study  
04:07:21 3 comparing a combination drug regimen of a checkpoint  
04:07:24 4 inhibitor and TKI drug versus sunitinib?

04:07:26 5 A. No. There were other studies that had reported out  
04:07:33 6 pembrolizumab plus axitinib, which was a keynote study. And  
04:07:38 7 then nivolumab plus axitinib, and sort of simultaneously was  
04:07:42 8 a study using the tyrosine kinase lenvatinib with the  
04:07:48 9 pembrolizumab.

04:07:49 10 Q. Have those TKI and IO combination regimens also shown  
04:07:54 11 superiority against sunitinib?

04:07:56 12 A. Yes, they have.

04:07:57 13 Q. And just to make sure it's clear for the record, what  
04:08:01 14 is an IO?

04:08:03 15 Was that referred to?

04:08:03 16 A. Yeah, that's an immuno oncology agent.

04:08:08 17 Q. And so that's a checkpoint inhibitor?

04:08:09 18 A. That's a checkpoint inhibitor.

04:08:11 19 Q. So was there anything new or unexpected about the  
04:08:14 20 fact that cabozantinib plus nivolumab combination therapy  
04:08:19 21 performed better than sunitinib alone in the CheckMate  
04:08:21 22 study?

04:08:22 23 A. No, I think there was already a lead-in that -- that  
04:08:25 24 there was evidence that -- well, first of all, to just take  
04:08:28 25 a step back. We all -- even we knew going in that immune

Mega - Direct

04:08:33 1 checkpoint inhibitors as a single-class therapy was very  
04:08:38 2 active in renal cell carcinoma, almost to the extent of, you  
04:08:44 3 know, speaking to it as ground-breaking activity because of  
04:08:47 4 the potential durable responses.

04:08:51 5 So, then, the addition of a tyrosine kinase  
04:08:53 6 inhibitor to get what scientifically we believed is a  
04:08:57 7 synergistic effect by blocking angiogenesis, affecting  
04:09:03 8 immune modulation and then adding on top of that an immune  
04:09:06 9 checkpoint inhibitor, I think was -- it was expected that  
04:09:11 10 this combination was going to give us better response rates,  
04:09:17 11 and it was evident that that was happening even before the  
04:09:20 12 CheckMate 9ER study reported out.

04:09:24 13 Q. Now, shifting to second-line treatment of RCC.

04:09:29 14 Dr. George identified cabozantinib as an option to treat  
04:09:32 15 patients for that category.

04:09:37 16 Do you recall that?

04:09:37 17 A. Yes.

04:09:38 18 Q. Are there other recommended options that physicians  
04:09:42 19 use in order to treat patients in that category?

04:09:45 20 A. Yes, I think if we look again at the NCCN guidelines.

04:09:51 21 Q. Sure.

04:09:51 22 A. You see that --

04:09:52 23 Q. That's PTX-528, Page 16.

04:09:57 24 Okay. Go ahead.

04:09:58 25 A. And we can see in those, I think, exceedingly

Mega - Direct

04:10:04 1 decreasing number of people who are -- who have not received  
04:10:08 2 immune checkpoint inhibitor therapy we then have the option  
04:10:11 3 of adding an immune checkpoint inhibitor. And then the  
04:10:15 4 people that, I think, is now the larger category, the ones  
04:10:19 5 that have received prior immune oncology therapy, we can see  
04:10:24 6 that there are four different tyrosine kinase -- tyrosine  
04:10:28 7 kinase therapies that are recommended.

04:10:31 8 Q. Do you recall Dr. George showed the METEOR study that  
04:10:34 9 tested cabozantinib as subsequent-line RCC therapy?

04:10:37 10 A. Yes, I do.

04:10:38 11 Q. Could you briefly remind us what that study showed?

04:10:41 12 A. Yeah. So the METEOR study was a Phase 3 randomized  
04:10:46 13 control trial comparing patients who had received at least  
04:10:52 14 one prior VEGF inhibitor therapy or tyrosine kinase  
04:10:58 15 inhibitor therapy and randomized them to compare  
04:11:01 16 cabozantinib not to another tyrosine kinase inhibitor, but  
04:11:04 17 to an mTOR inhibitor everolimus.

04:11:08 18 Q. Has cabozantinib been tested head to head against any  
04:11:11 19 TKIs for second-line treatment of RCC?

04:11:14 20 A. No, it has not.

04:11:15 21 Q. Dr. George also talked about the CONTACT-03 study.  
04:11:18 22 Can you remind us what the objective of that study was?

04:11:21 23 A. Yeah, the CONTACT-03 study was a study that was to  
04:11:30 24 answer a very important question that -- many of us had  
04:11:35 25 wondered if continuing -- continuing immune checkpoint

Mega - Direct

04:11:39 1 inhibitor therapy after you failed the regimen was still  
04:11:43 2 beneficial say if you've changed the partner, the tyrosine  
04:11:46 3 kinase inhibitor, and this was a study of continuation of  
04:11:50 4 immune checkpoint inhibitor therapy with a TKI, namely,  
04:11:54 5 cabozantinib versus just TKI therapy as monotherapy. And so  
04:11:59 6 the aim of the study was really to look at the benefit of  
04:12:03 7 continuing the immune checkpoint inhibitor, and there was no  
04:12:06 8 benefit in continuing it. And it was more toxic.

04:12:12 9 Q. Dr. Mega, in your opinion, is there a -- was there a  
04:12:15 10 long-felt unmet need for additional or improved treatment  
04:12:20 11 options for treating patients with RCC in a first or  
04:12:24 12 second-line therapy?

04:12:29 13 Strike that. Let me ask that --

04:12:33 14 In your opinion, does there remain a long-felt  
04:12:43 15 and unmet need today for additional or improved treatment  
04:12:46 16 options for treating patients with RCC in the first or  
04:12:50 17 subsequent lines?

04:12:50 18 A. I agree with Dr. George that the need remains for us  
04:12:56 19 to continue to try to build on the therapies that have  
04:13:01 20 advanced our options for treatment. So, yes, I still  
04:13:05 21 believe there is a an unmet need in the treatment for  
04:13:10 22 advanced renal cell carcinoma.

04:13:12 23 Q. How does cabozantinib's toxicity profile compare to  
04:13:16 24 other TKIs?

04:13:17 25 A. As a class of agents, they have their issues with

Mega - Direct

04:13:23 1 toxicity and patients usually will be experiencing side  
04:13:28 2 effects and that includes cabozantinib.

04:13:30 3 Q. Now, Dr. George provided an opinion on what he termed  
04:13:34 4 clinical success.

04:13:35 5 Did you hear that testimony?

04:13:36 6 A. I did.

04:13:38 7 Q. And he talked about his personal experience with his  
04:13:40 8 patients. How does your experience with cabozantinib or  
04:13:44 9 cabozantinib compare?

04:13:45 10 A. Like many of the tyrosine kinase inhibitors available  
04:13:50 11 for therapy, I've seen patients individually benefit and  
04:13:57 12 some benefit significantly, and that's what cabozantinib and  
04:14:02 13 a number of other agents -- as we have listed.

04:14:05 14 But I've also seen it not -- them not work,  
04:14:09 15 including cabozantinib, and, unfortunately, a large number  
04:14:12 16 of patients. And I've seen them have significant toxicity  
04:14:16 17 in a lot of patients.

04:14:19 18 Q. So with respect to your opinions on the objective  
04:14:22 19 indicia that you addressed, what is your opinion as to  
04:14:25 20 whether Cabometyx represents a different kind of treatment  
04:14:30 21 in the treatment of RCC?

04:14:31 22 A. It's my opinion that it does not represent a  
04:14:34 23 different kind of treatment. There remains an unmet need  
04:14:38 24 that it represents an incremental therapeutic growth and is  
04:14:45 25 really just a difference in degree rather than a difference

Mega - Cross

04:14:49 1 in kind.

04:14:50 2 MR. COOPER: Thank you, Dr. Mega. I pass the  
04:14:52 3 witness.

04:15:00 4 THE COURT: So, before you begin, Doctor, so is  
04:15:03 5 it your opinion that there's been a long-felt, unmet need  
04:15:07 6 basically for a long period of time?

04:15:10 7 THE WITNESS: For advanced renal cell carcinoma?  
04:15:14 8 Through my career, yes.

04:15:15 9 THE COURT: And so -- but your opinion is  
04:15:18 10 Cabometyx didn't meet it?

04:15:20 11 THE WITNESS: No. Cabometyx didn't meet it.  
04:15:24 12 And I think the major advancement has been in  
04:15:30 13 immunotherapeutics, not just for renal cell carcinoma, but  
04:15:34 14 for a whole host of malignancies because of the ability to  
04:15:38 15 get these very durable responses with treatment or that can  
04:15:42 16 last for years.

04:15:44 17 THE COURT: All right. Thank you. Go ahead.

04:15:44 18 CROSS-EXAMINATION

04:15:44 19 BY MS. WIGMORE:

04:15:47 20 Q. Good afternoon, Dr. Mega. You have prescribed  
04:15:49 21 Cabometyx to treat patients with advanced renal cell  
04:15:52 22 carcinoma; correct?

04:15:53 23 A. Yes, I have.

04:15:54 24 Q. And you do not dispute that Cabometyx had clinical  
04:15:57 25 success in some patients; correct?

Mega - Cross

04:15:59 1 A. No, I -- I agree that it did.

04:16:01 2 Q. You have observed Cabometyx improve outcomes for  
04:16:05 3 certain patients; correct?

04:16:06 4 A. I have similar to other TKIs, yes.

04:16:10 5 Q. And you continue to prescribe Cabometyx today;  
04:16:12 6 correct?

04:16:13 7 A. I do along with other TKIs yes.

04:16:16 8 Q. You would not continue to prescribe an oncology  
04:16:19 9 therapy that was not effective; correct?

04:16:21 10 A. No, I would not.

04:16:24 11 Q. Multiple characteristics can contribute to the  
04:16:26 12 clinical success of a drug product; correct?

04:16:29 13 A. I'm not sure I understand the multiple -- what  
04:16:35 14 multiple characteristics we're speaking of, but I could -- I  
04:16:38 15 could see how they could contribute to the success, yes.

04:16:41 16 Q. Consistent dosage is critical to patient treatment;  
04:16:44 17 correct?

04:16:45 18 A. Are you speaking about consistent absorption of a  
04:16:51 19 drug or -- when you say dosage, because every drug has a  
04:16:55 20 consistent dose. So, I would say correct, yes.

04:16:59 21 Q. Now, having a drug product optimized to promote  
04:17:03 22 absorption of the drug substance can be critical to the  
04:17:05 23 success of a cancer therapy; correct?

04:17:07 24 A. I think consistency in all absorption is important,  
04:17:12 25 correct.

Mega - Cross

04:17:12 1 Q. A cancer therapy would not be useful if it were  
04:17:16 2 packaged in a drug product that prevented its absorption in  
04:17:19 3 the patient's body; correct?

04:17:21 4 A. No, you would need to get the absorbed -- the drug  
04:17:25 5 absorbed for it to be useful, yes.

04:17:27 6 Q. A successful cancer therapy requires a compound that  
04:17:31 7 remains stable during the drug manufacturing process;  
04:17:34 8 correct?

04:17:34 9 A. I have limited knowledge about manufacturing, but I  
04:17:40 10 would say that stability would be important, yes.

04:17:43 11 Q. Preventing degradation of a drug substance is  
04:17:45 12 necessary in order to administer the drug; correct?

04:17:48 13 A. Again, the manufacturing process is not -- in my area  
04:17:54 14 of expertise but I think that would be important to have an  
04:17:57 15 effective drug, yes.

04:17:58 16 Q. A genotoxic impurity can lead to secondary cancer;  
04:18:03 17 correct?

04:18:03 18 A. Yes, it can.

04:18:04 19 Q. It is important to reduce genotoxic impurities in  
04:18:08 20 drug development; correct?

04:18:10 21 A. I believe it's uniformly important not just with  
04:18:15 22 tyrosine kinase inhibitors, but a whole host of agents, yes.

04:18:19 23 Q. If a patient is on a particular drug for a longer  
04:18:23 24 duration, the risk of any genotoxic impurities goes on for a  
04:18:28 25 longer period of time; correct?



Mega - Cross

04:18:29 1 A. Yes, that's correct.

04:18:31 2 Q. Now, resistance occurs when a patient stops  
04:18:34 3 responding to a particular therapy; correct?

04:18:36 4 A. Well, or does -- yeah, resistance would be not  
04:18:41 5 responding. Refractory would be never responding.

04:18:45 6 Q. And every day in your practice, you see patients that  
04:18:47 7 have developed drug resistance; correct?

04:18:50 8 A. Yes, I do.

04:18:52 9 Q. Having second and third-line therapies available is a  
04:18:55 10 very important option for individuals suffering from  
04:18:59 11 advanced renal cell carcinoma; correct?

04:19:01 12 A. That is correct.

04:19:04 13 Q. The treatment that might work best for one patient  
04:19:07 14 will not necessarily work best for another; correct?

04:19:10 15 A. Generally correct. I mean, there are -- sometimes  
04:19:16 16 the context is that changing a drug category, not just  
04:19:22 17 changing a drug within a category is a more preferable way  
04:19:27 18 to manage subsequent therapies.

04:19:29 19 Q. It is helpful for oncologists to have multiple  
04:19:32 20 therapies available to treat patients; correct?

04:19:34 21 A. It is helpful, yes.

04:19:37 22 Q. Now, you testified about the NCCN guidelines. For  
04:19:41 23 people who cannot tolerate immuno-oncology drugs, Cabometyx  
04:19:45 24 is an important first-line option; correct?

04:19:48 25 A. Cabo -- Cabometyx and all of the tyrosine kinase

Mega - Cross

04:19:53 1 inhibitors that were in recommended options would be  
04:19:58 2 considered options, yes.

04:19:59 3 Q. Cabometyx is the only preferred option for the  
04:20:03 4 unfavorable risk patients who cannot tolerate  
04:20:06 5 immuno-oncology; correct?

04:20:08 6 A. Speaking to the NCCN guidelines?

04:20:11 7 Q. Yes.

04:20:11 8 A. Yes.

04:20:13 9 Q. Now, your opinion is that Cabometyx offers a  
04:20:15 10 difference in degree, but not a difference in kind; is that  
04:20:19 11 right?

04:20:19 12 A. Yes, it is.

04:20:19 13 Q. A treatment's ability to extend the overall survival  
04:20:23 14 of a cancer patient can be a difference in kind in some  
04:20:27 15 circumstances; correct?

04:20:28 16 A. In -- I think there are noteworthy circumstances  
04:20:34 17 where that is true, but a lot of agents that are -- are  
04:20:41 18 brought into the marketplace do show these smaller benefits  
04:20:46 19 that are worthwhile, but don't represent a difference in  
04:20:49 20 kind.

04:20:50 21 Q. Every single month of increased survival matters to a  
04:20:53 22 patient; correct?

04:20:53 23 A. That could be a profound ethical discussion. I would  
04:21:00 24 say to you that a lot of factors play into that, including  
04:21:07 25 quality of life. Existential pain because, you know, you're

Mega - Cross

04:21:12 1 dying plays into that. So, I think that it's a much more  
04:21:16 2 complicated answer than yes or no.

04:21:19 3 Q. Fair enough.

04:21:20 4 You don't dispute that Cabometyx can extend a  
04:21:23 5 patient's life while maintaining quality of life, at least  
04:21:26 6 in some circumstances; correct?

04:21:27 7 A. Yes, I agree.

04:21:29 8 MS. WIGMORE: Thank you. No further questions.

04:21:31 9 THE COURT: All right. Anything more,  
04:21:33 10 Mr. Cooper?

04:21:33 11 MR. COOPER: No, thank you.

04:21:35 12 THE COURT: All right. Dr. Mega, thank you.  
04:21:37 13 Watch your step stepping down.

04:21:39 14 MR. BOYLE: Good afternoon, Your Honor. Kevin  
04:21:51 15 Boyle on behalf of Defendant, MSN. Defendants call their  
04:21:57 16 next witness, Dr. DeForest McDuff.

04:21:59 17 THE COURT: All right. Thank you.

04:22:02 18 MR. BOYLE: And we have some binders, as well,  
04:22:04 19 to bring up.

04:22:06 20 DEPUTY CLERK: Please state and spell your full  
04:22:14 21 name for the record.

04:22:14 22 THE WITNESS: Robert DeForest McDuff.

04:22:19 23 R-O-B-E-R-T. D-E, capital F, O-R-E-S-T. M-C, capital D,  
04:22:25 24 U-F-F.

04:22:25 25 ROBERT DeFOREST McDUFF, the witness herein,

McDuff - Direct

04:22:25 1 after having been affirmed, was examined and testified as  
04:22:33 2 follows:

04:22:33 3 THE WITNESS: Yes, I do.

04:22:33 4 DIRECT EXAMINATION

04:22:35 5 BY MR. BOYLE:

04:22:35 6 Q. Good afternoon, Dr. McDuff. Could you please  
04:22:41 7 introduce yourself?

04:22:41 8 A. Good afternoon. My name is DeForest McDuff, and I'm  
04:22:43 9 an economist.

04:22:44 10 Q. Have you prepared slides to assist with your  
04:22:46 11 testimony today?

04:22:47 12 A. Yes. They're on the screen.

04:22:49 13 Q. All right. Dr. McDuff, I briefly want to talk about  
04:22:52 14 your professional background.

04:22:53 15 MR. BOYLE: Can we pull up DTX-530?

04:22:53 16 BY MR. BOYLE:

04:22:57 17 Q. Dr. McDuff, what is DTX-530?

04:23:00 18 A. This is a copy of my professional CV.

04:23:02 19 Q. And does it accurately reflect your professional  
04:23:05 20 qualifications?

04:23:06 21 A. Yes, it does.

04:23:09 22 MR. BOYLE: Can we go to DDX-2?

04:23:09 23 BY MR. BOYLE:

04:23:12 24 Q. Dr. McDuff, can you please provide the Court with a  
04:23:15 25 brief description of your educational background?

McDuff - Direct

04:23:18 1 A. Sure. I have bachelor degrees in economics and  
04:23:20 2 mathematics from the University of Maryland and I have a  
04:23:24 3 master's degree and Ph.D. in economics from Princeton.

04:23:26 4 Q. And can you also describe your professional  
04:23:28 5 background?

04:23:28 6 A. Yes. I work as an economic consultant at a firm  
04:23:31 7 called Insight Economics, which I founded in 2017. And I'm  
04:23:35 8 an assistant teaching professor in the Department of  
04:23:37 9 Economics at UNC, Chapel Hill.

04:23:39 10 Q. And can you provide a summary of your experience  
04:23:44 11 evaluating economics of the pharmaceutical industry?

04:23:45 12 A. Yes. I worked on more than 75 cases on topics of  
04:23:49 13 commercial success, irreparable harm, damages, product  
04:23:52 14 launches, and other issues.

04:23:54 15 Q. And have you previously testified in this Court?

04:23:56 16 A. Yes.

04:23:57 17 MR. BOYLE: Your Honor, Defendants proffer  
04:23:59 18 Dr. DeForest McDuff as an expert in economics and commercial  
04:24:03 19 success.

04:24:06 20 MS. PIROZZOLO: No objection.

04:24:07 21 THE COURT: All right. You may proceed.

04:24:08 22 BY MR. BOYLE:

04:24:08 23 Q. Dr. McDuff, were you here in the courtroom for  
04:24:13 24 Mr. Tate's testimony?

04:24:14 25 A. Yes, I was.

McDuff - Direct

04:24:15 1 Q. And did you prepare a slide summarizing the testimony  
04:24:19 2 you plan to offer today?

04:24:21 3 A. Yes.

04:24:22 4 MR. BOYLE: Can we go to DDX-3?

04:24:22 5 BY MR. BOYLE:

04:24:26 6 Q. Having listened to Mr. Tate's testimony, can you  
04:24:28 7 please provide an overview of the opinions that you'll be  
04:24:31 8 offering?

04:24:32 9 A. Sure. I have three main opinions. The first is that  
04:24:35 10 there's no commercial success due to blocking disincentives.  
04:24:38 11 The second is that there's -- he has performed no analysis  
04:24:41 12 of other patents which pertains to nexus. And the third is  
04:24:43 13 that his analysis of the product success itself is  
04:24:46 14 incomplete.

04:24:48 15 Q. All right. Let's start with that first point, no  
04:24:51 16 commercial success due to blocking disincentives.

04:24:55 17 Could you please explain the idea behind  
04:24:58 18 blocking and market exclusivity as it relates to commercial  
04:25:01 19 success?

04:25:02 20 A. Sure. Blocking via earlier patents or FDA  
04:25:06 21 exclusivity deters other from pursuing the claimed subject  
04:25:10 22 matter, even if it's obvious. And so the inference about  
04:25:13 23 obviousness from commercial success is no longer present if  
04:25:16 24 there's a blocking patent or exclusivity.

04:25:19 25 Q. And is that -- has that kind of deterrence been

McDuff - Direct

04:25:23 1 present in this case?

04:25:23 2 A. Yes.

04:25:26 3 MR. BOYLE: Let's pull up DTX-013.

04:25:26 4 BY MR. BOYLE:

04:25:31 5 Q. Dr. McDuff, what is DTX-013?

04:25:34 6 A. This is the '473 patent, which relates to the  
04:25:37 7 cabozantinib compound. We heard about this in testimony  
04:25:40 8 this week.

04:25:41 9 Q. And is this one of the patents at issue in the first  
04:25:43 10 case?

04:25:43 11 A. Yes.

04:25:46 12 MR. BOYLE: Let's pull up DTX-192.

04:25:46 13 BY MR. BOYLE:

04:25:50 14 Q. Dr. McDuff, what is DTX-192?

04:25:53 15 A. This is the international publication date of the  
04:25:57 16 application ending in 140A-2. We also heard about this this  
04:26:01 17 week relating to the cabozantinib compound where the  
04:26:05 18 publication leading to the '473 was published in April 2005.

04:26:10 19 Q. So, this is the earlier application that eventually  
04:26:14 20 led to the '473?

04:26:16 21 A. Yes.

04:26:19 22 MR. BOYLE: Can we pull up DDX-4.

04:26:19 23 BY MR. BOYLE:

04:26:21 24 Q. Let's start at the top here of DDX-4.

04:26:25 25 Dr. McDuff, can you please explain what you're

McDuff - Direct

04:26:27 1 showing in the first red line?

04:26:29 2 A. Yes. This is a timeline of the relevant events,  
04:26:33 3 which I think helps illustrate the blocking analysis.

04:26:36 4 From 2002 to 2010, at the top, you can see  
04:26:39 5 collaborations that Exelixis had with GlaxoSmithKline and  
04:26:44 6 Bristol Myers Squibb. Those were exclusive collaborations  
04:26:48 7 that were announced in Exelixis' SEC filings.

04:26:51 8 Q. And that collaboration started in October 2002?

04:26:55 9 A. Yes.

04:26:57 10 Q. And let's go to the second red line.

04:26:59 11 What are you showing in the second red line?

04:27:01 12 A. This is the timeline for the '473 patent in the  
04:27:06 13 cabozantinib compound claiming priority in September 2003  
04:27:10 14 and the publication date we just talked about in April 2005.

04:27:15 15 Q. All right. And in blue, what are you showing in  
04:27:18 16 blue?

04:27:18 17 A. These are the patents-in-suits in the current case,  
04:27:21 18 the malate salt patents with priority in -- claimed in 2009.  
04:27:25 19 And the '349 patent with priority claimed in 2011.

04:27:29 20 Q. And in green, what are you showing in green?

04:27:32 21 A. The green are the sales of the products that were  
04:27:35 22 discussed by Mr. Tate, Cabometyx and Cometriq.

04:27:38 23 Q. So, what does this timeline show about blocking and  
04:27:42 24 exclusivity as it relates to commercial success in this  
04:27:45 25 case?



McDuff - Direct

04:27:46 1 A. Because of the earlier development and the earlier  
04:27:50 2 intellectual property, even if the sales were successful  
04:27:54 3 there's no inference to be made about whether others would  
04:27:57 4 have developed the malate salt patents or the '349 patent  
04:28:00 5 had they been obvious. There's just no inference one way or  
04:28:03 6 the other because of the earlier intellectual property and  
04:28:05 7 collaborations.

04:28:07 8 Q. So looking at the time between April 2005 and  
04:28:12 9 August 2009, which is the time between the publication of  
04:28:15 10 the application, which is DTX-192, and the issuance of the  
04:28:21 11 '473 patent, would other entities have been aware that  
04:28:25 12 Exelixis was seeking patent protection related to  
04:28:28 13 cabozantinib?

04:28:28 14 A. Yes. And that would have provided a deterrence based  
04:28:33 15 on the patent issuing at a future point in time.

04:28:35 16 Q. And does the priority date of both the malate salt  
04:28:39 17 patents and the '349 patent fall within this blocking period  
04:28:43 18 that you described?

04:28:43 19 A. Yes, that's right.

04:28:47 20 Q. And how do you evaluate the strength of the economic  
04:28:52 21 deterrence that this blocking period would provide?

04:28:56 22 A. I evaluated economic factors that come from the  
04:28:59 23 *Acorda* case from the Federal Circuit.

04:29:02 24 MR. BOYLE: All right. Let's turn to the next  
04:29:03 25 slide, DDX-5.

McDuff - Direct

04:29:06 1 Q. Dr. McDuff, what are the *Acorda* factors?

04:29:09 2 A. The *Acorda* factors are economic factors that are  
04:29:12 3 outlined in the -- in the case opinion which relate to how  
04:29:17 4 strong the disincentives are -- how strong are the  
04:29:19 5 disincentives for others to be deterred from that  
04:29:22 6 development.

04:29:22 7 Q. Can you please briefly explain the role that each of  
04:29:26 8 these factors played in this case?

04:29:27 9 A. Yes. Number one, there's been no successful  
04:29:30 10 challenge of the '473 patent that's been asserted against  
04:29:33 11 entities like MSN.

04:29:34 12 Number two, there's been no development of  
04:29:36 13 others in the 2009 to 2011 time frame that I've seen.

04:29:41 14 Number three, the invention race with Exelixis  
04:29:44 15 is important because the holder of the patent is also  
04:29:47 16 pursuing the product. So, a third-party developer would be  
04:29:51 17 concerned that even if they were going to pursue this  
04:29:53 18 development, they would lose the invention race to Exelixis  
04:29:56 19 and its partners.

04:29:57 20 Number four on licensing. There's no evidence  
04:29:59 21 that there's a good licensing opportunity here, not with the  
04:30:02 22 exclusive collaborations with GSK and BMS.

04:30:06 23 And overall, number five, there's low economic  
04:30:09 24 opportunity for others in light of the blocking patent.

04:30:12 25 Q. So after evaluating these five *Acorda* factors, what

McDuff - Direct

04:30:16 1 did you conclude with respect to the blocking deterrence  
04:30:19 2 here?

04:30:19 3 A. There's a strong deterrence here.

04:30:23 4 Q. And how does that relate to commercial success?

04:30:26 5 A. As a result, commercial success, even if it's true  
04:30:29 6 for the product, doesn't provide an inference of  
04:30:32 7 nonobviousness for the patents.

04:30:34 8 MR. BOYLE: All right. We can take that down  
04:30:36 9 for a moment.

04:30:36 10 BY MR. BOYLE:

04:30:37 11 Q. Let's talk about your second opinion, no nexus  
04:30:41 12 analysis.

04:30:43 13 Dr. McDuff, can you briefly explain what does it  
04:30:45 14 mean to analyze nexus as it relates to commercial success?

04:30:49 15 A. Sure. Nexus is about the degree of connection  
04:30:52 16 between what is the claimed subject matter and the product  
04:30:55 17 performance.

04:30:56 18 Q. And do you think Mr. Tate has provided an adequate  
04:31:00 19 evaluation of nexus in this case?

04:31:02 20 A. No, not in my opinion.

04:31:03 21 Q. And why not?

04:31:04 22 A. Because he's only analyzed the patents at issue in  
04:31:07 23 this case. He doesn't weigh them against the other patents  
04:31:09 24 that are listed in the FDA Orange Book for the products at  
04:31:13 25 issue.

McDuff - Direct

04:31:13 1 Q. All right. Let's take a look at those patents.

04:31:15 2 MR. BOYLE: Can we pull up DDX-6?

04:31:15 3 BY MR. BOYLE:

04:31:20 4 Q. And are these the patents listed in the Orange Book  
04:31:23 5 that you're referring to?

04:31:24 6 A. Yes, that's right.

04:31:25 7 Q. And these refer to the Cabometyx product?

04:31:28 8 A. Yes. These are the patents listed for Cabometyx in  
04:31:31 9 the FDA Orange Book. You'll see there are 11 here; there  
04:31:34 10 are four non-asserted patents, there are three patents from  
04:31:37 11 the prior case, and there are four patents asserted in the  
04:31:39 12 current case.

04:31:40 13 Q. And did Mr. Tate's analysis of nexus evaluate all of  
04:31:44 14 these patents?

04:31:45 15 A. No, not at all.

04:31:47 16 Q. And why is that a problem?

04:31:48 17 A. Because we're trying to figure out if there is some  
04:31:52 18 degree of market success what inference of obviousness to  
04:31:56 19 draw on the patents-in-suit or some other patents.

04:31:59 20 So, without evaluating the contributions of the  
04:32:02 21 claimed subject matter compared to what else covers the  
04:32:05 22 product, there's no way to draw a nexus or an inference that  
04:32:08 23 others would have developed the claimed subject matter  
04:32:10 24 sooner.

04:32:11 25 Q. And did you testify last year in the first trial, the

McDuff - Direct

04:32:14 1 MSN 1 trial?

04:32:15 2 A. Yes.

04:32:16 3 Q. And how did Mr. Tate's nexus analysis from that trial  
04:32:20 4 regarding the '473 patent compare to his nexus analysis  
04:32:23 5 here?

04:32:23 6 A. It was exactly the same. The product analysis was  
04:32:27 7 exactly the same, the nexus analysis was the same, and I  
04:32:29 8 think it shows a lack of differentiation for which patents  
04:32:33 9 we're drawing an inference to.

04:32:36 10 Q. For the '349 patent at issue in this case, what's  
04:32:39 11 your understanding of the opinions offered by MSN's experts?

04:32:44 12 A. My understanding from Dr. Donovan is that a  
04:32:48 13 formulation could be created without the glidant as part of  
04:32:51 14 the '349 patent. And so as a result, it's not necessary for  
04:32:54 15 the formulation that's claimed.

04:32:56 16 Q. So, why does that matter for nexus, that the  
04:32:59 17 '349 patent is not necessary?

04:33:02 18 A. Because if you could get similar chemical performance  
04:33:06 19 or clinical performance, and then ultimately market  
04:33:09 20 performance without the '349 patent, then that's a lack of  
04:33:11 21 nexus.

04:33:12 22 MR. BOYLE: All right. Let's go to DDX-7.

04:33:12 23 BY MR. BOYLE:

04:33:16 24 Q. And are you showing the same thing with respect to  
04:33:19 25 the patents listed in the Orange Book for Cometriq?

McDuff - Direct

04:33:22 1 A. Yes, that's right. There are seven of them.

04:33:24 2 Q. And is there the same lack of nexus issue for

04:33:27 3 Cometriq?

04:33:28 4 A. Yes. It's basically unevaluated by Plaintiff's

04:33:31 5 commercial success analysis.

04:33:33 6 Q. And could you explain again why that is a problem?

04:33:35 7 A. Because you risk drawing an inference to patents that

04:33:39 8 are not relevant. There needs to be some sort of weighing

04:33:42 9 of the importance of these various patents in driving the

04:33:44 10 commercial performance.

04:33:47 11 Q. So, overall, what did you conclude about Mr. Tate's

04:33:50 12 nexus analysis?

04:33:51 13 A. It's not sufficient to conclude nexus, in my opinion.

04:33:55 14 Q. All right. Let's talk about your third opinion, the

04:33:58 15 product performance.

04:34:00 16 MR. BOYLE: Can we go to DDX-8?

04:34:00 17 BY MR. BOYLE:

04:34:04 18 Q. What is your view of Mr. Tate's market analysis of

04:34:10 19 Cabometyx and the Cometriq product performance?

04:34:12 20 A. That it's very high level and incomplete. As you can

04:34:16 21 see, I've got three opinions here relating to definition of

04:34:19 22 success, development costs, and the market shares.

04:34:21 23 Q. All right. Let's take those one at a time. What do

04:34:23 24 you mean by no definition of success?

04:34:25 25 A. Here, I'm referring to the sales being presented in

McDuff - Direct

04:34:30 1 isolation. We saw a bar chart of the sales over time, but  
04:34:34 2 there's no comparison to know whether those are high,  
04:34:37 3 average, low for this kind of product.

04:34:40 4 Same thing with number of patients. We heard  
04:34:42 5 55,000 patients, but I don't know if that's high, I don't  
04:34:45 6 know if that's low. There's no definition of what  
04:34:48 7 constitutes success here. And, ultimately, no evaluation of  
04:34:52 8 whether others would have developed this product sooner.

04:34:54 9 THE COURT: I'm sorry, when you are saying high  
04:34:56 10 or low, high or low relevant to what?

04:34:58 11 THE WITNESS: That's the point. There's no bar  
04:35:01 12 or benchmark or comparison to say this level of sales or  
04:35:05 13 this level of patients would motivate others to pursue this  
04:35:08 14 product.

04:35:11 15 THE COURT: All right.

04:35:12 16 BY MR. BOYLE:

04:35:12 17 Q. And turning to your second point, no development  
04:35:17 18 cost. What do you mean by no development costs?

04:35:20 19 A. Here, I'm talking about the investment to bring the  
04:35:23 20 product to market. In pharmaceuticals, it's -- for  
04:35:27 21 evaluating success, it's really a weighing of the many years  
04:35:30 22 of investment, clinical trials, with the sales and profits.

04:35:34 23 But in Mr. Tate's analysis, there was no  
04:35:36 24 evaluation of profits in comparison with the investment  
04:35:41 25 required to bring this product to market. So there's no

McDuff - Direct

04:35:43 1 evaluation of a return on investment or whether it's  
04:35:45 2 successful or not.

04:35:47 3 Q. And third, wide range of market shares, could you  
04:35:52 4 explain what that means?

04:35:53 5 A. Yes. So in Mr. Tate's report, he had many market  
04:35:56 6 definitions and market shares. He presented two or three of  
04:35:59 7 them today, but there were over 20 in his expert report,  
04:36:03 8 some are very high, some are very low, in the single digits.

04:36:06 9 Here, again, there's no explanation or  
04:36:09 10 definition of what constitutes success for this kind of  
04:36:12 11 product.

04:36:14 12 Q. So, taken together, what's your opinion of Mr. Tate's  
04:36:18 13 product analysis?

04:36:19 14 A. In my view, it's incomplete, it's not enough to draw  
04:36:22 15 a conclusion on commercial success one way or the other.

04:36:25 16 Q. All right.

04:36:26 17 MR. BOYLE: Let's go to DDX-9.

04:36:26 18 BY MR. BOYLE:

04:36:28 19 Q. Can you please re-summarize for the Court your three  
04:36:31 20 main points again?

04:36:32 21 A. Yeah. Primarily, there's no inference of commercial  
04:36:35 22 success due to the blocking disincentives, I think that's  
04:36:38 23 the main point, due to the earlier IP. In my opinion,  
04:36:41 24 plaintiffs also have not shown that there's a nexus or that  
04:36:44 25 the product itself has been successful.



McDuff - Direct

04:36:46 1 Q. And what conclusion should be drawn from these three  
04:36:49 2 points?

04:36:49 3 A. No commercial success, in my view.

04:36:53 4 MR. BOYLE: Thank you, Dr. McDuff. I pass the  
04:36:57 5 witness, but first defendants would like to introduce  
04:37:00 6 DTX-530.

04:37:02 7 THE COURT: All right. Admitted without  
04:37:03 8 objection?

04:37:05 9 MS. PIROZZOLO: No objection, Your Honor.

04:37:06 10 THE COURT: All right.

04:37:06 11 (DTX Exhibit No. 530 was admitted into  
04:37:07 12 evidence.)

04:37:07 13 THE COURT: Actually, Dr. McDuff, the point you  
04:37:12 14 were making about the nexus and the glidant and the -- I  
04:37:16 15 think it's the '439 patent, but the one with the essentially  
04:37:20 16 free, can you just try running that one by me again?

04:37:25 17 THE WITNESS: Sure. As I understand it from  
04:37:28 18 Dr. Donovan, technically you could have a formulation or a  
04:37:32 19 process that produces a formulation with or without the  
04:37:35 20 glidant, one of the claimed elements, as I understand it.

04:37:38 21 So, if that's true, you don't need to practice  
04:37:41 22 the patent to get the same chemical, clinical, and market  
04:37:44 23 performance, then there's no nexus to the patent.

04:37:48 24 THE COURT: And so, does that depend because, of  
04:37:51 25 course -- well, maybe this is -- "of course" is the wrong

Duff - Cross

04:38:00 1 words.

04:38:04 2 Dr. Donovan's opinion is there isn't a glidant  
04:38:07 3 in the MSN product. Exelixis' opinion is there is. Your  
04:38:18 4 opinion on that depends on Dr. Donovan being right rather  
04:38:22 5 than Exelixis' technical experts?

04:38:25 6 THE WITNESS: I think that's right. It depends  
04:38:27 7 on whether you could have a similarly performing product  
04:38:30 8 without the '349 patent.

04:38:34 9 THE COURT: All right.

04:38:34 10 All right. Ms. Pirozzolo, you've got two  
04:38:37 11 minutes max.

04:38:38 12 MS. PIROZZOLO: Thank you, Your Honor.

04:38:40 13 CROSS-EXAMINATION

04:38:41 14 BY MS. PIROZZOLO:

04:38:44 15 Q. Dr. McDuff, you're not disputing that Exelixis'  
04:38:48 16 product, Cabometyx, practices the asserted patents; correct?

04:38:53 17 A. I'm not assessing that one way or the other.

04:38:56 18 Q. You don't dispute that tens of thousands of patients  
04:38:59 19 have taken Cabometyx and Cometriq instead of many other  
04:39:03 20 drugs approved for treatment of cancer; correct?

04:39:06 21 A. I'm not disputing the numbers, no.

04:39:09 22 Q. Okay. You agree that revenues reflect physicians'  
04:39:13 23 decisions to prescribe a drug to patients; correct?

04:39:16 24 A. Yes. Downstream, first it's prescriptions and then  
04:39:21 25 that's realized in revenues.

Duff - Cross

04:39:23 1 Q. And you don't dispute Mr. Tate's summary of the  
04:39:26 2 revenues for Cabometyx; correct?

04:39:28 3 A. I'm not disputing the figures, no.

04:39:30 4 Q. Okay. Now, your blocking analysis pertains to the  
04:39:34 5 effect of the '473 on the patents-in-suit; correct?

04:39:39 6 A. Yes.

04:39:40 7 Q. Okay. You understand that MSN's defense is  
04:39:45 8 obviousness-type double patenting, not obviousness, for the  
04:39:48 9 malate salt patents; correct?

04:39:50 10 A. I understand that's one defense, yes.

04:39:53 11 Q. Okay. And you understand that the '473 is not prior  
04:39:58 12 art to the crystalline malate salt patents; correct?

04:40:00 13 A. I'm not sure.

04:40:03 14 MS. PIROZZOLO: I have no further questions,  
04:40:05 15 Your Honor.

04:40:05 16 THE COURT: All right. Thank you. Any  
04:40:06 17 redirect.

04:40:07 18 MR. BOYLE: No redirect, Your Honor.

04:40:08 19 THE COURT: All right. Dr. McDuff, you can step  
04:40:10 20 down. Watch your step. Okay.

04:40:12 21 THE WITNESS: Thank you, Your Honor.

04:40:14 22 THE COURT: All right. I guess we're done.

04:40:16 23 MR. COOPER: Yeah, Your Honor, can I move in  
04:40:22 24 from Dr. Mega's examination DTX-536.

04:40:27 25 MS. WIGMORE: No objection.

Duff - Cross

04:40:28 1 THE COURT: All right.

04:40:29 2 MR. COOPER: And defendants rest their case.

04:40:31 3 Thank you.

04:40:32 4 THE COURT: All right. So that's admitted  
04:40:34 5 without objection.

04:40:34 6 (DTX Exhibit No. 536 was admitted into  
04:40:34 7 evidence.)

04:40:36 8 THE COURT: I'm not entirely sure, but I think  
04:40:38 9 I've been admitting some of these things multiple times  
04:40:41 10 without objection.

04:40:42 11 Okay. So, in any event, we're done with the  
04:40:45 12 testimony; right?

04:40:47 13 MR. COOPER: Yes, Your Honor.

04:40:47 14 MS. PIROZZOLO: Yes, Your Honor.

04:40:48 15 THE COURT: Okay. So, we've got closing  
04:40:53 16 arguments tomorrow morning at 9:30, and I want to talk about  
04:40:57 17 that in a minute.

04:40:59 18 I can't recall in terms of the briefing to  
04:41:05 19 follow, is that something that has been worked out or is  
04:41:09 20 that something that's still to be determined?

04:41:13 21 MR. PRUSSIA: I think, Your Honor, we have been  
04:41:15 22 so caught up in the trial that we haven't had a chance to  
04:41:17 23 discuss that. I think myself and Mr. Cooper and the others  
04:41:19 24 can probably caucus on it this evening and come to you  
04:41:23 25 tomorrow.

Duff - Cross

04:41:24 1 THE COURT: Yeah, so that would be better. I'd  
04:41:26 2 rather have you caucus first. All right. In terms of  
04:41:28 3 closing argument. So, how much -- as I recall, at least  
04:41:37 4 it's partly because it's what I usually do. When we talk  
04:41:41 5 about closing argument, I said maybe 30 minutes, maybe  
04:41:44 6 45 minutes, maybe somewhere in between. At least I would  
04:41:48 7 expect that I said that.

04:41:53 8 What do you-all think.

04:41:55 9 MR. PRUSSIA: Your Honor, we would request  
04:41:58 10 45 minutes, if that works for the Court.

04:42:00 11 MR. LOMBARDI: And that's fine with us, too,  
04:42:02 12 Your Honor.

04:42:02 13 THE COURT: All right. Well, so I'm willing to  
04:42:05 14 do 45 minutes a side. But one of the things that I want to  
04:42:12 15 make sure that I'm not getting is an argument that's really  
04:42:19 16 as though somebody is just reading a brief to me. So, I've  
04:42:25 17 been trying to think. You know, earlier I tried to take  
04:42:29 18 care of that concern by limiting the number of slides, but  
04:42:36 19 that didn't really seem to necessarily achieve my objective.

04:42:40 20 So, I don't want you to read your arguments to  
04:42:49 21 me. I certainly expect you to have notes, topics, things to  
04:42:57 22 remind you of, you know, what it is you want to talk about,  
04:43:01 23 but I want to see your eyes looking at me for most of the  
04:43:06 24 time, okay?

04:43:09 25 And I don't mind if you have -- I don't require

Duff - Cross

04:43:13 1 that you have any slides. But particularly -- and I'm not  
04:43:18 2 sure how actually important it is in this case. But  
04:43:22 3 particularly, if, you know, you want to be making arguments  
04:43:24 4 about text, I don't object to having the text up there, and  
04:43:32 5 I leave it to your judgment if you think there's a few  
04:43:35 6 slides I really need to see.

04:43:37 7 But I -- again, I want to be looking mostly at  
04:43:41 8 you at the podium. And I can't look at the slide at the  
04:43:44 9 same time. So, if you need to -- if you need slides, yeah,  
04:43:49 10 use slides in moderation.

04:43:56 11 And so partly -- partly I thought that maybe --  
04:44:00 12 maybe I was shooting myself in the foot earlier because I  
04:44:04 13 said, okay, 30 minutes. And then you just felt like there  
04:44:06 14 was so much stuff. And by -- when I say you, I don't mean  
04:44:09 15 any of you personally, but that lawyers thought there was so  
04:44:13 16 much important stuff they had to tell me that they then, you  
04:44:18 17 know, write down 45 minutes worth of stuff and deliver it in  
04:44:22 18 30 minutes. So, by giving you 45 minutes, hoping that won't  
04:44:27 19 happen.

04:44:27 20 In any event, that's my hopes about that.

04:44:31 21 Is there anything else we need to discuss right  
04:44:35 22 now or otherwise I'll let you go and get ready for tomorrow  
04:44:41 23 and do whatever else you need to do. And we can talk about  
04:44:47 24 the briefing after you've done the arguments.

04:44:51 25 MR. PRUSSIA: Nothing for Plaintiffs,

Duff - Cross

04:44:53 1 Your Honor.

04:44:53 2 MR. LOMBARDI: Nothing for Defendants,

04:44:54 3 Your Honor.

04:44:54 4 THE COURT: Okay. All right. Well, thank you

04:44:56 5 very much. And I will see you tomorrow.

04:45:03 6 DEPUTY CLERK: All rise.

7 (Court was recessed at 4:45 p.m.)

8 I hereby certify the foregoing is a true and

9 accurate transcript from my stenographic notes in the

10 proceeding.

11 /s/ Heather M. Triozzi

12 Certified Merit and Real-Time Reporter

13 U.S. District Court.

14

15

16

17

18

19

20

21

22

23

24

25